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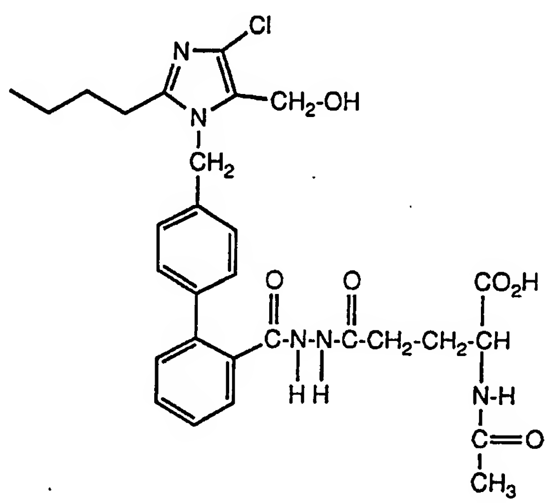

(57) Abstract

Renal-selective compounds are described which, in one embodiment, are prodrugs preferentially converted in the kidney to compounds capable of blocking angiotensin II (AII) receptors. These prodrugs are conjugates formed from two components, namely, a first component provided by an AII antagonist compound and a second component which is capable of being cleaved from the first component when both components are chemically linked within the conjugate. The two components are chemically linked by a bond which is cleaved selectively in the kidney, for example, by an enzyme. The liberated AII antagonist compound is then available to block AII receptors within the kidney. Conjugates of particular interest are glutamyl derivatives of biphenylmethyl 1H-substituted imidazole compounds, of which N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl] [1,1'-biphenyl]-2-yl]carbonyl]hydrazide shown above is an example.

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RENAL-SELECTIVE ANGIOTENSIN II ANTAGONISTS FOR TREATMENT OF HYPERTENSION

Field of the Invention

This invention is in the field of cardiovascular therapeutics and relates to a class of compounds useful in control of hypertension. Of particular interest is a class of prodrugs of angiotensin II antagonists which, when selectively hydrolyzed in the kidney, provide hypertension control.

Background of the Invention

The renin-angiotensin system is one of the hormonal mechanisms involved in regulation of pressure/volume homeostasis and in expression of hypertension. Activation of the renin-angiotensin cascade begins with renin secretion from the juxtaglomerular apparatus of the kidney and culminates in the formation of angiotensin II, an octapeptide which is the primary active species of this system. Angiotensin II is a potent vasoconstrictor agent and also produces other physiological effects such as promoting aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, increasing vasopressin secretion, causing positive cardiac inotropic effect and modulating other hormonal systems.

Previous studies have shown that antagonizing angiotensin II at its receptors is a viable approach to inhibit the renin-angiotensin system, given the pivotal role of this octapeptide which mediates the actions of the renin-angiotensin system through interaction with various tissue receptors. There are several known angiotensin II antagonists, most of which are peptidic in nature. Such peptidic compounds are of limited use due to their lack of

oral bioavailability or their short duration of action. Also, commercially-available peptidic angiotensin II antagonists (e.g., Saralasin) have a significant residual agonist activity which further limit their therapeutic application.

Non-peptidic compounds with angiotensin II antagonist properties are known. For example, the sodium salt of 2-n-butyl-4-chloro-1-(2-chlorobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [P. C. Wong et al, J. Pharmacol. Exp. Ther., 247(1), 1-7 (1988)]. Also, the sodium salt of 2-butyl-4-cholorо-1-(2-nitrobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [A. T. Chiu et al, European J. Pharmacol., 157, 3121 (1988)]. A family of 1-benzylimidazole-5-acetate derivatives has been shown to have competitive angiotensin II antagonist properties [A. T. Chiu et al, J. Pharmacol. Exp. Ther., 250(3), 867-874 (1989)]. U.S. Patent No. 4,816,463 to Blankey et al describes a family of 4,5,6,7-tetrahydro-1H-imidazo(4,5-c)-tetrahydro-pyridine derivatives useful as antihypertensives, some of which are reported to antagonize the binding of labelled angiotensin II to rat adrenal receptor preparation and thus cause a significant decrease in mean arterial blood pressure in conscious hypertensive rats. EP No. 253,310, published 20 January 1988, describes a series of aralkyl imidazole compounds, including in particular a family of biphenylmethyl substituted imidazoles, as antagonists to the angiotensin II receptor. EP No. 323,841 published 12 July 1989 describes four classes of angiotensin II antagonists, namely, biphenylmethylpyrroles, biphenylmethylpyrazoles, biphenylmethyl-1,2,3-triazoles and biphenylmethyl 4-substituted-4H-1,2,4-triazoles, including the compound 3,5-

dibutyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-4H-1,2,4-triazole. U.S. Patent No. 4,880,804 to Carini et al describes a family of biphenylmethylbenzimidazole compounds as angiotensin II receptor blockers for use in treatment of hypertension and congestive heart failure.

One disadvantage of these angiotensin II antagonist compounds is that the desired hypertension-reducing effect may be offset by hypotension-induced compensatory stimulation of the renin-angiotensin system or stimulation of the sympathetic nervous system, either of which may result in promotion of sodium and water retention. Also, some angiotensin II antagonists may have toxicological effects systemically which precludes their use at doses necessary to be effective in reducing blood pressure.

To avoid such systemic side effects, drugs may be targetted to the kidney by creating a conjugate compound that would be a renal-specific prodrug containing the targetted drug modified with a chemical carrier moiety. Cleavage of the drug from the carrier moiety by enzymes predominantly localized in the kidney releases the drug in the kidney. Gamma glutamyl transpeptidase and acylase are examples of such cleaving enzymes found in the kidney which have been used to cleave a targetted drug from its prodrug carrier within the kidney.

Renal targetted prodrugs are known for delivery of a drug selectively to the kidney. For example, the compound L-γ-glutamyl amide of dopamine when administered to dogs was reported to generate dopamine *in vivo* by specific enzymatic cleavage by γ-glutamyl transpeptidase [J. J. Kyncl et al, *Adv. Biosc.*, **20**, 369-380 (1979)]. In another study, γ-glutamyl and N-acyl-γ-glutamyl derivatives of the anti-bacterial compound sulfamethoxazole were shown to deliver relatively high

concentrations of sulfamethoxazole to the kidney which involved enzymatic cleavage of the prodrug by acylamino acid deacylase and γ-glutamyl transpeptidase [M. Orlowski et al, J. Pharmacol. Exp.Ther., 212, 167-172 (1980)]. The N-γ-glutamyl derivatives of 2-, 3-, or 4-aminophenol and p-fluoro-L-phenylalanine have been found to be readily solvolyzed *in vitro* by γ-glutamyl transpeptidase [S.D.J. Magnan et al, J. Med. Chem., 25, 1018-1021 (1982)]. The hydralazine-like vasodilator 2-hydrazino-5-n-butylpyridine (which stimulates guanylate cyclase activity) when substituted with the N-acetyl-γ-glutamyl residue resulted in a prodrug which provided selective renal vasodilation [K. G. Hofbauer et al, J. Pharmacol. Exp. Ther., 212, 838-844 (1985)]. The dopamine prodrug γ-L-glutamyl-L-dopa ("gludopa") has been shown to be relatively specific for the kidney and to increase renal blood flow, glomerular filtration and urinary sodium excretion in normal subjects [D. P. Worth et al, Clin. Sci., 69, 207-214 (1985)]. In another study, gludopa was reported to be an effective renal dopamine prodrug whose activity can be blocked by the dopa-decarboxylase inhibitor carbidopa [R. F. Jeffrey et al, Br. J. Clin. Pharmac., 25, 195-201 (1988)]. A class of 4-ureido derivatives of isoquinolin-3-ol has been investigated for renal specific effects such as increases in renal vasodilation and renal blood flow [R. M. Kanojia et al, J. Med. Chem., 32, 990-997 (1989)].

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Fig. 1 is a graph showing reduction in mean arterial pressure by intravenous administration of a conjugate of the invention to a spontaneously hypertensive rat.

Fig. 2 is a graph showing angiotensin II pressor response in a spontaneously hypertensive rat infused by

intravenous administration with a conjugate of the invention over a period of three days.

Fig. 3 is a graph showing urinary sodium excretion response to angiotensin II infusion in concious normotensive rats followed by administration of a saline vehicle, an angiotensin II antagonist, or a renal-selective conjugate of the invention.

Fig. 4 is a graph showing mean arterial pressure response to angiotensin II infusion in conscious normotensive rats followed by administration of a saline vehicle, an angiotensin II antagonist, or a renal-selective conjugate of the invention..

DESCRIPTION OF THE INVENTION

Treatment of chronic hypertension or sodium-retaining disorders such as congestive heart failure, cirrhosis and nephrosis, may be accomplished by administering to a susceptible or afflicted subject a therapeutically-effective amount of a renal-selective prodrug capable of causing blood-pressure reducing effects by selective action in the kidney. An advantage of such renal-selective prodrug therapy resides in reduction or avoidance of adverse side effects associated with systemically-acting drugs.

Advantages of a renal-selective antihypertensive compound are several. First, the renal-selective compound is targetted at those pathophysiological mechanisms which occur primarily in the kidney. Second, the regulation of other organ systems is unaffected; thus, normal physiological regulation of other organ systems is maintained. Third, fewer side-effects may be anticipated, since the compound remains

inactive until cleaved in the kidneys. Similarly, fewer negative drug-drug interactions may be anticipated. Finally, since a renal-selective accumulation of active compound may occur, which is not dependent on plasma levels of the parent compound, lower doses of the renal-selective compound compared to active parent compound may be used.

A renal-selective prodrug is provided by a conjugate comprising a residue of an angiotensin II antagonist compound, which conjugate is renal selective. The conjugate will typically comprise a first component and a second component connected together by a cleavable or hydrolyzable bond. The term "renal-selective", as used to characterize a conjugate of the invention, embraces any of the following four pharmacological events: (1) the conjugate is selectively taken up by the kidney and is selectively cleaved in the kidney; (2) the conjugate is not taken up selectively by the kidney, but is selectively cleaved in the kidney; (3) the conjugate is selectively taken up by the kidney and then cleaved in the kidney; or (4) where the conjugate itself is active as an angiotensin II antagonist, the conjugate is selectively taken up by the kidney without cleavage of the hydrolyzable bond.

The first component of a conjugate of the invention is a residue derived from an antagonist compound capable of inhibiting angiotensin II (AII) receptors, especially those AII receptors located in the kidney. The second residue is capable of being cleaved from the first residue preferentially. Cleaving of the first and second residues may be accomplished by a variety of mechanisms. For example, the bond may be cleaved by an enzyme in the kidney.

The residue providing the first component may be characterized as the "AII antagonist active" residue. Such

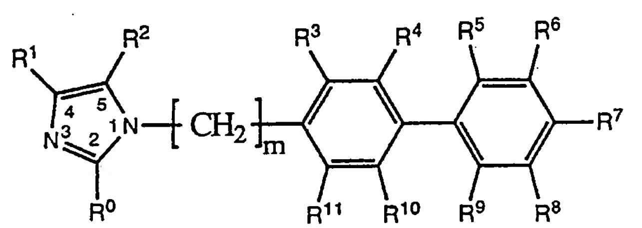
"active" residue may be provided by a compound having AII antagonist activity or by a metabolite of such compound having AII antagonist activity. The residue providing the second component may be characterized in being capable of forming a cleavable bond connecting the "active" first residue and the second residue. Such bond is cleavable by an enzyme located in the kidney. In a preferred embodiment, this cleavable bond is typically a hydrolyzable amide bond, that is, a bond between a carbonyl-terminated moiety and a reactive nitrogen-terminated moiety, such as an amino-terminated moiety, which may be cleaved by an enzyme found in the kidney, but which is not cleaved substantially by enzymes located in other organs or tissues of the body. Preferred bond-cleaving enzymes would be found predominantly in the kidney.

The conjugate containing the residue of an AII antagonist compound and containing the cleavable fragment or residue may possess AII antagonist activity comparable to, or more than, or less than, the AII antagonist compound which forms the conjugate. In one embodiment of the invention, the conjugate will have AII receptor blocking activity comparable to the AII antagonist component forming the conjugate. In another embodiment of the invention, the conjugate will have AII receptor blocking activity less than the AII receptor blocking activity forming the conjugate. One advantage of such differential activity between the conjugate and the AII antagonist component is that certain side effects associated with non-renal, systemic AII receptor blocking may be avoided or reduced. For example, at least one conjugate of the invention has been found to have a very large differential in AII receptor blocking activities between the conjugate and the AII antagonist component forming the conjugate. Such differential activity is advantageous in that therapeutically-effective antihypertensive doses of the conjugate may be administered to give renal-selective AII receptor blocking

action resulting from kidney-specific enzyme hydrolysis or metabolism of the conjugate to free the active AII receptor blocker within the kidney. Inasmuch as this renal-selective conjugate has relatively low AII receptor blocking activity, compared to the AII receptor compound forming the conjugate, this conjugate will have fewer adverse side effects associated with unwanted systemic interaction with non-renal AII receptors such as found in the vascular bed.

DETAILED DESCRIPTION OF THE INVENTION

The first residue of the conjugate may be selected from any class of compounds, or metabolites thereof, having angiotensin II antagonist activity. An example of one such class of angiotensin II antagonist compounds is provided by a class of biphenylmethyl 1H-substituted-1,3-imidazole compounds defined by Formula I:

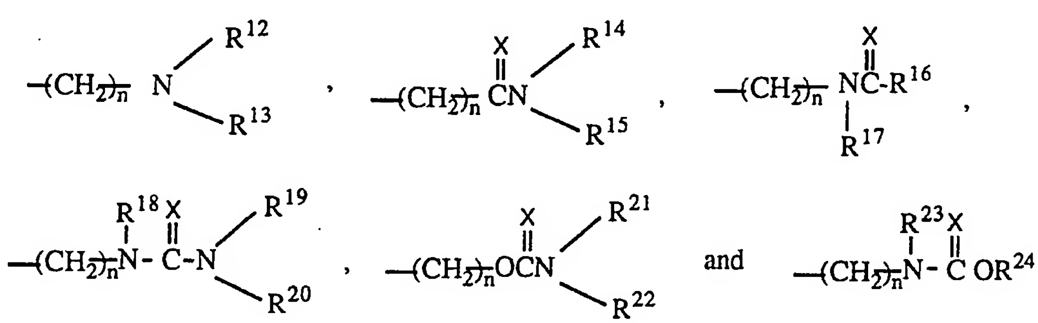


(I)

wherein m is a number selected from one to four, inclusive;

wherein each of R^0 through R^{11} is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl,

mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing groups has one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{16} and R^{17} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

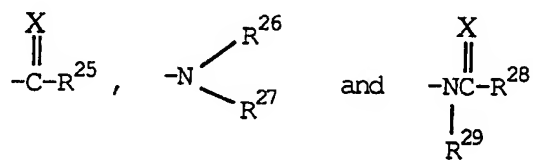
and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

$$-Y_nA$$

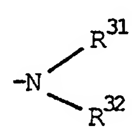
wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing R^1 through R^{24}, Y and A

groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula

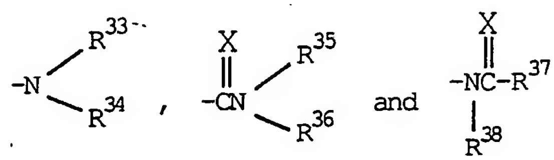


wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR^{30} and



wherein D is selected from oxygen atom and sulfur atom and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further

independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each of R^{33}, R^{34}, R^{35}, R^{36}, R^{37} and R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R^{26} and R^{27} taken together and R^{28} and R^{29} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{26} and R^{27} taken together and R^{31} and R^{32} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

Conjugates of the invention are therapeutically effective in treatment of cardiovascular disorders by acting directly, or by providing cleavable components selected from Formula I compounds which act directly, as antagonists to, or blockers of, the angiotensin II (AII) receptor. Thus, conjugates of Formula I would be therapeutically effective in treatment of cardiovascular disorders or would be precursors to, or prodrugs of, therapeutically-effective compounds.

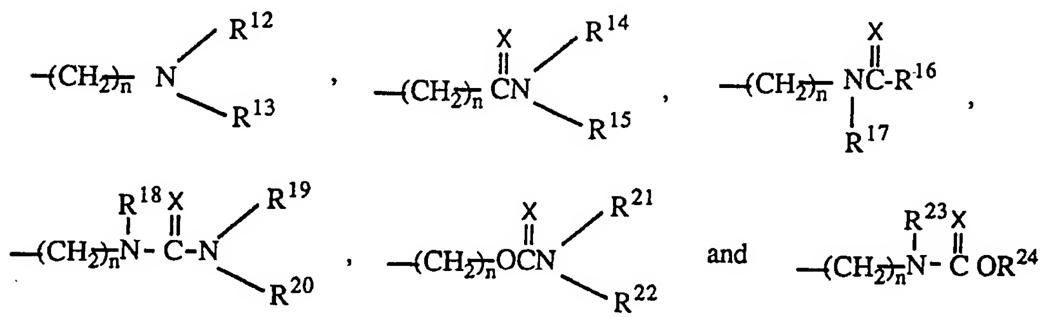
Preferred compounds of Formula I, from which a cleavable component may be selected, are all characterized in having a substituent, other than hydrido, at each of the four- and five-positions of the imidazole ring. Such substituents are selected from the aforementioned R^1 and R^2 groups.

The phrase "acidic group selected to contain at least one acidic hydrogen atom", as used to define the $-Y_nA$ moiety, is intended to embrace chemical groups which, when attached to any of the R^3 through R^{11} positions of Formula I, confers acidic character to the compound of Formula I. "Acidic character" means proton-donor capability, that is, the capacity of the compound of Formula I to be a proton donor in the presence of a proton-receiving substance such as water. Typically, the acidic group should be selected to have proton-donor capability such that the product compound of Formula I has a pK_a in a range from about one to about twelve. More typically, the Formula I compound would have a pK_a in a range from about two to about seven. An example of an acidic group containing at least one acidic hydrogen atom is carboxyl group (-COOH). Where n is zero and A is -COOH, in the $-Y_nA$ moiety, such carboxyl group would be attached directly to one of the R^3 through R^{11} positions. The Formula I compound may have one

$-Y_nA$ moiety attached at one of the R^3 through R^{11} positions, or may have a plurality of such $-Y_nA$ moieties attached at more than one of the R^3 through R^{11} positions, up to a maximum of nine such $-Y_nA$ moieties. There are many examples of acidic groups other than carboxyl group, selectable to contain at least one acidic hydrogen atom. Such other acidic groups may be collectively referred to as "bioisosteres of carboxylic acid" or referred to as "acidic bioisosteres". Specific examples of such acidic bioisosteres are described hereinafter. Compounds of Formula I having the $-Y_nA$ moiety attached at one of positions R^5, R^6, R^8 and R^9 would be expected to have preferred properties, while attachment at R^5 or R^9 would be more preferred.

A preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R^0 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothio-carbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto,

alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

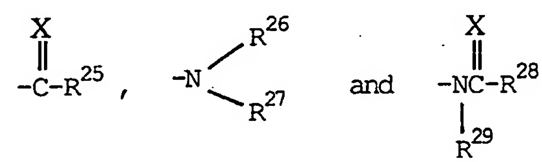
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

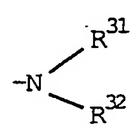
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula

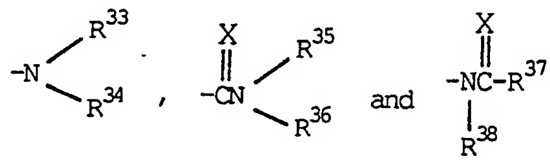


wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, and R^{30} is selected from hydrido, alkyl, cycloalkyl,

cycloalkylalkyl, aralkyl and aryl; wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

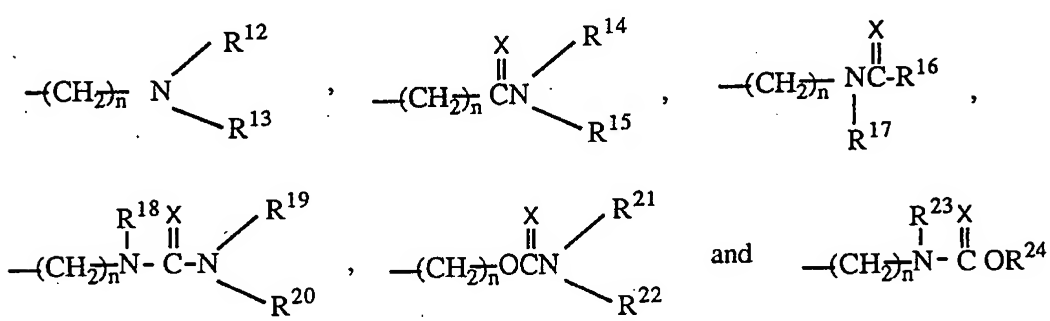
wherein each of R^{26} through R^{31} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A more preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R^0 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl,

alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalklylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen taom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

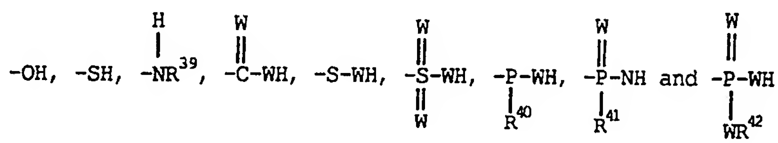
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

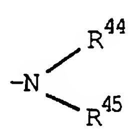
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{40}, R^{41}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39}, R^{40}, R^{41} and R^{42} may be further independently selected from amino radicals of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further

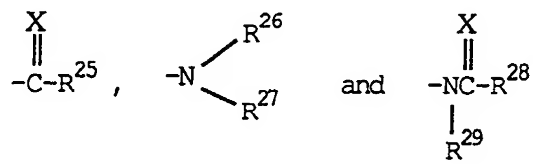
contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R^{40} and R^{41} may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

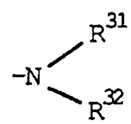
wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl,

carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR^{30} and



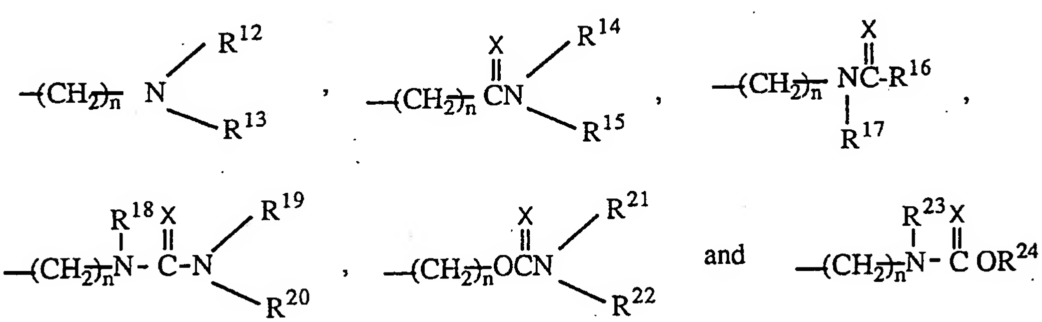
wherein D is selected from oxygen atom and sulfur atom, wherein R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

An even more preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R^0, R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

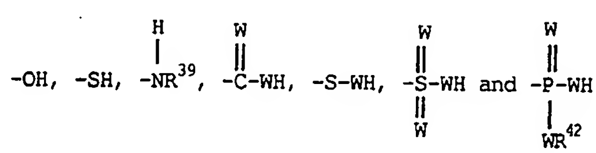
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

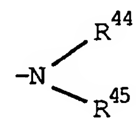
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl,

cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

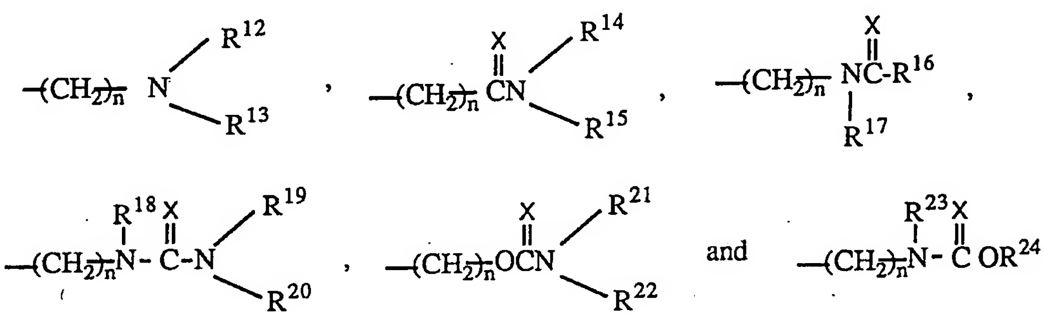
wherein each of R^1 through R^{24}, Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A highly preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R^0, R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl-

and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

$$-OH,\quad -SH,\quad -\overset{\displaystyle H}{\overset{|}{N}}R^{39},\quad -\overset{\displaystyle W}{\overset{\|}{C}}-WH,\quad -S-WH,\quad -\underset{\displaystyle W}{\underset{\|}{\overset{\displaystyle W}{\overset{\|}{S}}}}-WH \text{ and } -\underset{\displaystyle WR^{42}}{\underset{|}{\overset{\displaystyle W}{\overset{\|}{P}}}}-WH$$

wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula

$$-N\begin{matrix} \diagup R^{44} \\ \diagdown R^{45} \end{matrix}$$

wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form

a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

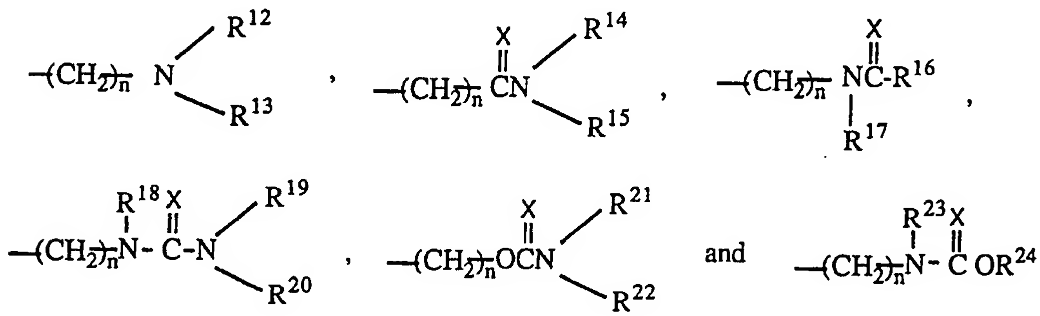
wherein each of R^1 through R^{24}, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

An even more highly preferred class of compounds within Formula I consists of those compounds wherein m is one; wherein R^0 is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of R^1 and R^2 is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl,

aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



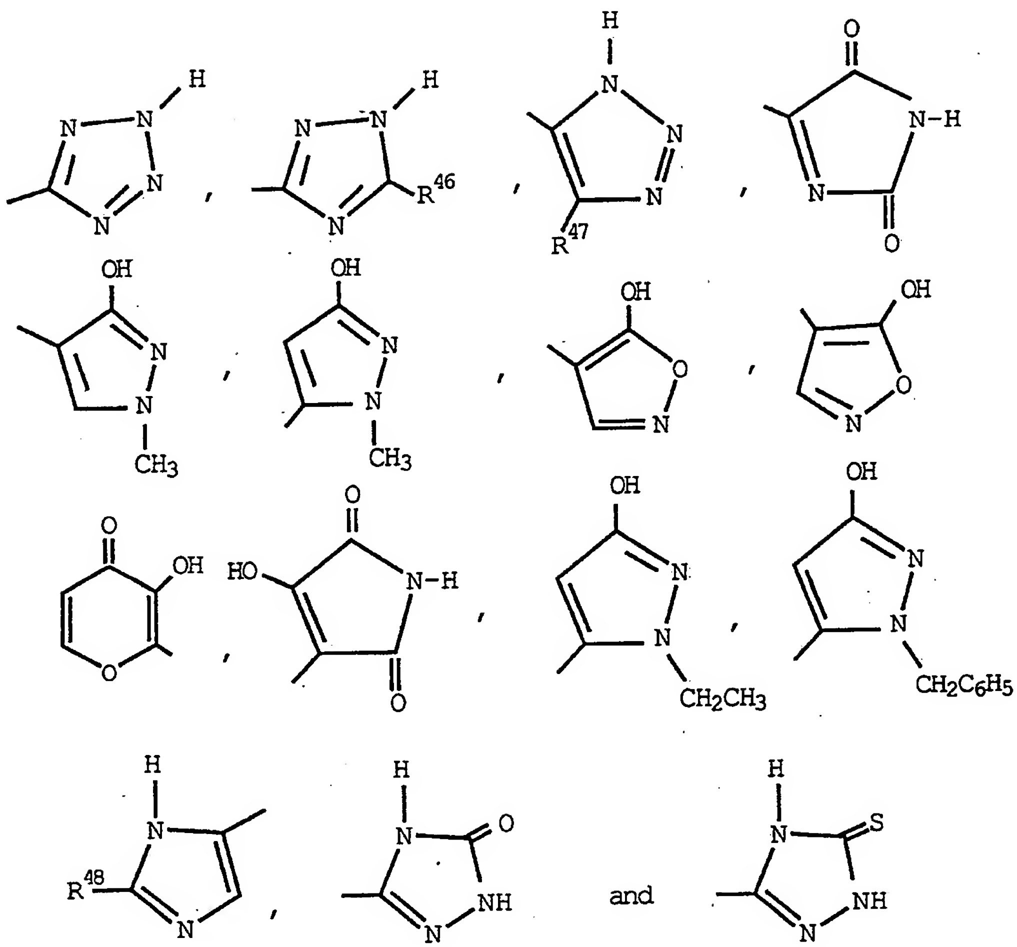
wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

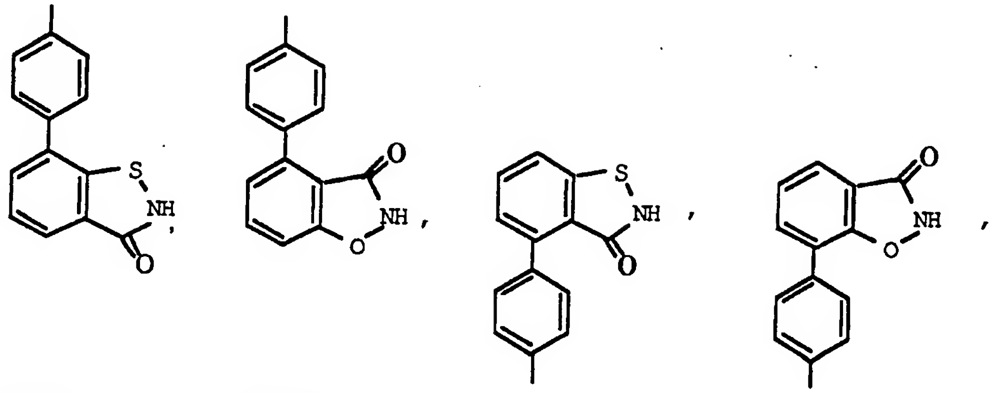
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

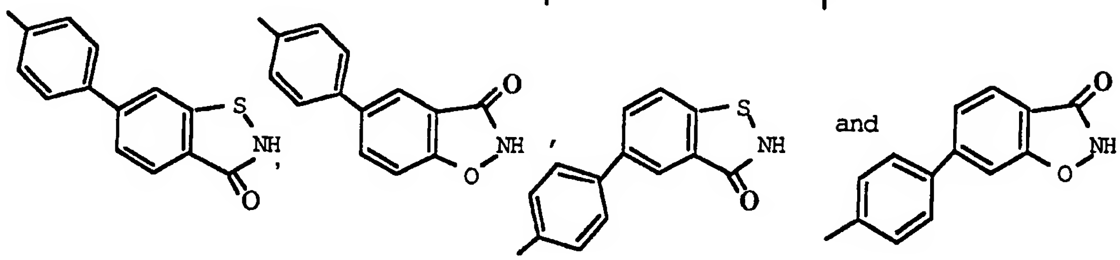
wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties consisting of CO_2H, CO_2CH_3, SH, CH_2SH, C_2H_4SH, PO_3H_2, $NHSO_2CF_3$, $NHSO_2C_6F_5$, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, $CONHOCH_3$, $CONHOC_2H_5$, $CONHCF_3$, OH, CH_2OH, C_2H_4OH, OPO_3H_2, OSO_3H ,



wherein each of R^{46}, R^{47} and R^{48} is independently selected from H, Cl, CN, NO_2, CF_3, C_2F_5, C_3F_7, CHF_2, CH_2F, CO_2CH_3, $CO_2C_2H_5$, SO_2CH_3, SO_2CF_3 and $SO_2C_6F_5$; wherein Z is selected from O, S, NR^{49} and CH_2; wherein R^{49} is selected from hydrido, CH_3 and $CH_2C_6H_5$; and wherein said acidic moiety may be a heterocyclic acidic group attached at any two adjacent positions of R^3 through R^{11} so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from

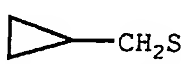


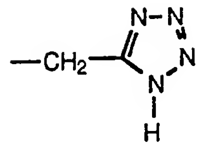


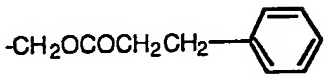
and the esters, amides and salts of said acidic moieties;

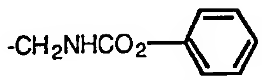
with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

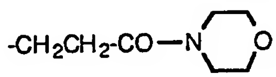
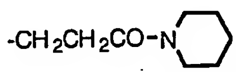
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest within Formula I consists of those compounds wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH{=}CH$, $C_3H_7(n)$, SC_3H_7, , , C_2H_5, $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9, , $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH-$; wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO,

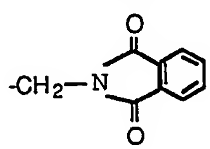
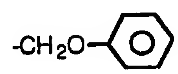
CH_2CO_2H, $CH(CH_3)CO_2H$, NO_2, Cl, ,

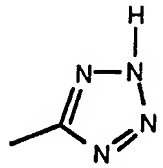
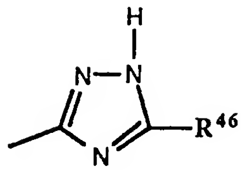
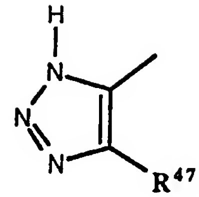
, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,

$-CH_2-NHCO_2C_2H_5$, , $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H,

, , $-CH_2CH_2CH_2CO_2H$,

$-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2OCSNHCH_3$, $-CH_2NHCSOC_3H_7$,

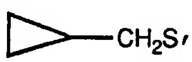
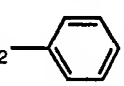
$-CH_2CH_2CH_2F$, $-CH_2ONO_2$, , $-CH_2SH$, , H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

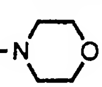
 ,  and 

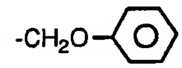
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

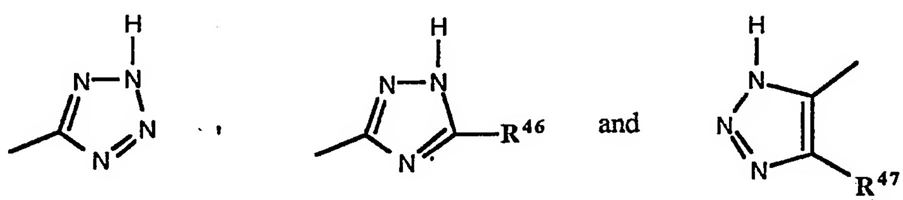
with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A class of compounds of more particular interest within Formula I consists of those compounds wherein m is one; wherein R^0 is selected from C_4H_9(n), $CH_3CH_2CH{=}CH$, C_3H_7(n), SC_3H_7, , , C_2H_5, C_5H_{11}(n), C_6H_{13}(n), SC_4H_9, , $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH-$; wherein R^1 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO, CH_2CO_2H, $CH(CH_3)CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$, $-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H,

$-CH_2CH_2-CO-$, $-CH_2CH_2CH_2CO_2H$,

$-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2CH_2CH_2F$, $-CH_2SH$ and ; wherein R^2 is selected from H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through R^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

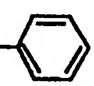
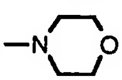
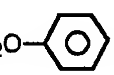


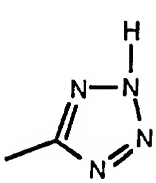
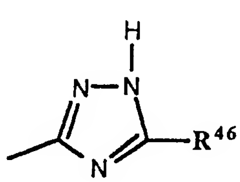
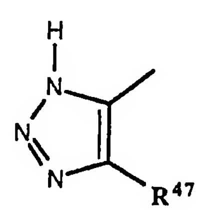
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A class of compounds of even more particular interest within Formula I consists of those compounds wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH{=}CH$,

$C_3H_7(N)$, SC_3H_7, , , C_2H_5, $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9, CH_2S, $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH-$; wherein R^1 is selected from H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO, CH_2CO_2H, $CH(CH_3)CO_2H$, , $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$, $-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H, $-CH_2CH_2-CO-$, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2CH_2CH_2F$, $-CH_2SH$ and $-CH_2O-$; wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

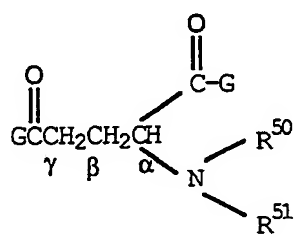
 ,  and 

wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

The second component of a conjugate of the invention is provided by a residue which forms a kidney-enzyme-cleavable amide bond with the residue of the first-component AII antagonist compound. Such residue is preferably selected from a class of compounds of Formula II:

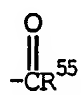


(II)

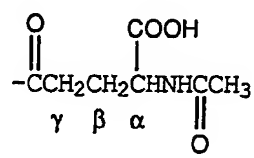
wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{52}$, $-SR^{53}$ and $>NR^{54}$ wherein each of R^{52}, R^{53} and R^{54} is independently selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

More preferred are compounds of Formula II wherein each G is hydroxy.

A more highly preferred class of compounds within Formula II consists of those compounds wherein each G is hydroxy; wherein R^{50} is hydrido; and wherein R^{51} is selected from

 wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

A most highly preferred compound of Formula II is N-acetyl-γ-glutamic acid which provides a residue for the second component of a conjugate of the invention as shown below:



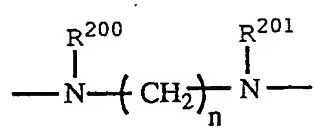
The phrase "terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino terminal moiety" characterizes a structural requirement for selection of a suitable angiotensin II antagonist compound as the "active" first residue of a conjugate of the invention. Such terminal amino moiety must be available to react with a terminal carboxylic moiety of the cleavable second residue to form a kidney-enzyme-specific hydrolyzable bond.

In one embodiment of the invention, the first component used to form a conjugate of the invention provides a first residue derived from an AII antagonist compound

containing a terminal primary or secondary amino moiety. Examples of such terminal amino moiety are amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups such as aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

In another embodiment of the invention, the first component used to form the conjugate of the invention provides a first residue derived from an AII antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety. An example of a moiety convertible to an amino terminal moiety is a carboxylic acid group reacted with hydrazine so as to convert the acid moiety to carboxylic acid hydrazide. The hydrazide moiety thus contains the terminal amino moiety which may then be further reacted with the carboxylic acid containing residue of the second component to form a hydrolyzable amide bond. Such hydrazide moiety thus constitutes a "linker" group between the first and second components of a conjugate of the invention.

Suitable linker groups may be provided by a class of diamino-terminated linker groups based on hydrazine as defined by Formula III:

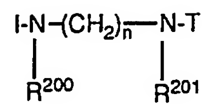


(III)

wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is

zero or a number selected from three through seven, inclusive. In Table I there is shown a class of specific examples of diamino-terminated linker groups within Formula III, identified as Linker Nos. 1-73. These linker groups would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of a carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE I



I = inhibitor
T = acetyl-γ-glutamyl

LINKER NO.	n	R^{200}	R^{201}
1	0	H	H
2	0	CH_3	H
3	0	C_2H_5	H
4	0	C_3H_7	H
5	0	$CH(CH_3)_2$	H
6	0	C_4H_9	H
7	0	$CH(CH_3)CH_2CH_3$	H
8	0	$C(CH_3)_3$	H
9	0	C_5H_9	H
10	0	C_6H_{11} (cyclo)	H
11	0	C_6H_5	H

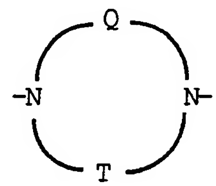
LINKER NO.	n	R^{200}	R^{201}
12	0	$CH_2C_6H_5$	H
13	0	H	CH_3
14	0	H	C_2H_5
15	0	H	C_3H_7
16	0	H	$CH(CH_3)_2$
17	0	H	C_4H_9
18	0	H	$CH(CH_3)CH_2CH_3$
19	0	H	$C(CH_3)_3$
20	0	H	C_5H_9
21	0	H	C_6H_{13}
22	0	H	C_6H_5
23	0	H	$CH_2C_6H_5$
24	0	H	C_6H_{11} (cyclo)
25	0	C_6H_{13}	H
26	0	CH_3	CH_3
27	0	C_2H_5	C_2H_5

LINKER NO.	n	R^{200}	R^{201}
28	0	C_3H_7	C_3H_7
29	0	$CH(CH_3)_2$	$CH(CH_3)_2$
30	0	C_4H_9	C_4H_9
31	0	$CH(CH_3)CH_2CH_3$	$CH(CH_3)CH_2CH_3$
32	0	$C(CH_3)_3$	$C(CH_3)_3$
33	0	C_5H_9	C_5H_9
34	0	C_6H_{13}	C_6H_{13}
35	0	C_6H_{11} (cyclo)	C_6H_{11} (cyclo)
36	0	C_6H_5	C_6H_5
37	0	$CH_2C_6H_5$	$CH_2C_6H_5$
38	3	H	H
39	3	CH_3	H
40	3	H	CH_3
41	3	C_6H_5	H
42	3	H	C_6H_5

LINKER NO.	n	R^{200}	R^{201}
43	3	CH_3	C_6H_5
44	3	C_6H_5	CH_3
45	3	$CH_2C_6H_5$	H
46	3	H	$CH_2C_6H_5$
47	4	H	H
48	4	CH_3	H
49	4	H	CH_3
50	4	C_6H_5	H
51	4	H	C_6H_5
52	4	CH_3	C_6H_5
53	4	C_6H_5	CH_3
54	4	$CH_2C_6H_5$	H
55	4	H	$CH_2C_6H_5$
56	5	H	H
57	5	CH_3	H
58	5	H	CH_3

LINKER NO.	n	R^{200}	R^{201}
59	5	C_6H_5	H
60	5	H	C_6H_5
61	5	CH_3	C_6H_5
62	5	C_6H_5	CH_3
63	5	$CH_2C_6H_5$	H
64	5	H	$CH_2C_6H_5$
65	6	H	H
66	6	CH_3	H
67	6	H	CH_3
68	6	C_6H_5	H
69	6	H	C_6H_5
70	6	CH_3	C_6H_5
71	6	C_6H_5	CH_3
72	6	$CH_2C_6H_5$	H
73	6	H	$CH_2C_6H_5$

Another class of suitable diamino terminal linker groups is defined by Formula IV:

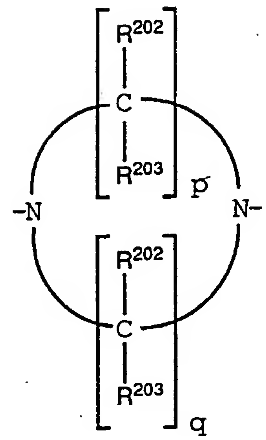


(IV)

wherein each of Q and T is one or more groups independently selected from

wherein each of R^{202} through R^{205} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

A preferred class of linker groups within Formula IV is defined by Formula V:

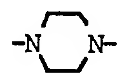


(V)

wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

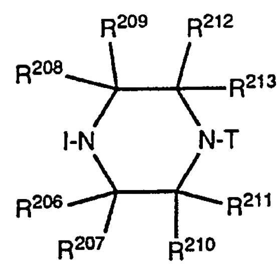
A more preferred class of linker groups of Formula V consists of divalent radicals wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive. Even more preferred are linker groups wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three. Most preferred is a linker group wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two; such most preferred linker

group is derived from a piperazinyl group and has the structure



In Table II there is shown a class of specific examples of cyclized, diamino-terminated linker groups within Formula V. These linker groups, identified as Linker Nos. 74-95, would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE II

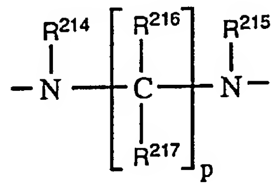


I = inhibitor
T = acetyl-γ-glutamyl

LINKER NO.	R^{206}	R^{207}	R^{208}	R^{209}	R^{210}	R^{211}	R^{212}	R^{213}
74	H	H	H	H	H	H	H	H
75	CH_3	H	H	H	H	H	H	H
76	H	H	H	H	CH_3	H	H	H
77	CH_3	H	H	H	CH_3	H	H	H
78	CH_3	H	CH_3	H	H	H	H	H
79	CH_3	H	H	H	H	H	CH_3	H
80	CH_3	CH_3	H	H	H	H	H	H
81	H	H	H	H	CH_3	CH_3	H	H
82	CH_3	CH_3	H	H	CH_3	CH_3	H	H
83	CH_3	CH_3	CH_3	CH_3	H	H	H	H

LINKER NO.	R^{206}	R^{207}	R^{208}	R^{209}	R^{210}	R^{211}	R^{212}	R^{213}
84	CH_3	CH_3	H	H	H	H	CH_3	CH_3
85	H	H	H	H	CH_3	CH_3	CH_3	CH_3
86	C_6H_5	H	H	H	H	H	H	H
87	H	H	H	H	C_6H_5	H	H	H
88	C_6H_5	H	H	H	C_6H_5	H	H	H
89	C_6H_5	H	H	H	H	H	C_6H_5	H
90	C_6H_5	H	C_6H_5	H	H	H	H	H
91	$CH_2C_6H_5$	H	H	H	H	H	H	H
92	H	H	H	H	$CH_2C_6H_5$	H	H	H
93	$CH_2C_6H_5$	H	H	H	$CH_2C_6H_5$	H	H	H
94	$CH_2C_6H_5$	H	H	H	H	H	$CH_2C_6H_5$	H
95	$CH_2C_6H_5$	H	$CH_2C_6H_5$	H	H	H	H	H

Another class of suitable diamino terminal linker groups is defined by Formula VI:



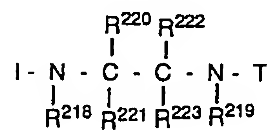
(VI)

wherein each of R^{214} through R^{217} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfino, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

A preferred class of linker groups within Formula VI consists of divalent radicals wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{62} and R^{63} is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three. A more preferred class of linker groups within Formula VI consists of divalent radicals wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido and alkyl; and wherein p is two. A specific example of a more preferred linker within Formula VI is the divalent radical ethylenediamino. In Table III there is shown a class of specific examples of diamino-terminated linker gorups within Formula VI. These linker groups, identified as Linker Nos. 96-134, would be suitable to

form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE III



I = inhibitor
G = acetyl-γ-glutamyl

LINKER NO.	R^{218}	R^{219}	R^{220}	R^{221}	R^{222}	R^{223}
96	H	H	H	H	H	H
97	H	H	H	H	H	CH_3
98	H	H	H	CH_3	H	H
99	H	H	H	CH_3	H	CH_3
100	CH_3	H	H	H	H	H
101	H	CH_3	H	H	H	H
102	H	H	H	H	CH_3	CH_3
103	H	H	CH_3	CH_3	H	H

LINKER NO.	R^{218}	R^{219}	R^{220}	R^{221}	R^{222}	R^{223}
104	CH_3	CH_3	H	H	H	H
105	H	H	H	H	H	C_6H_5
106	H	H	H	C_6H_5	H	H
107	H	H	H	C_6H_5	H	C_6H_5
108	C_6H_5	H	H	H	H	H
109	H	C_6H_5	H	H	H	H
110	H	H	H	H	C_6H_5	C_6H_5
111	H	H	C_6H_5	C_6H_5	H	H
112	C_6H_5	C_6H_5	H	H	H	H
113	H	H	H	H	H	C_2H_5
114	H	H	H	C_2H_5	H	H
115	H	H	H	C_2H_5	H	C_2H_5
116	C_2H_5	H	H	H	H	H
117	H	C_2H_5	H	H	H	H
118	H	H	H	H	C_2H_5	C_2H_5

LINKER NO.	R^{218}	R^{219}	R^{220}	R^{221}	R^{222}	R^{223}
119	H	H	C_2H_5	C_2H_5	H	H
120	C_2H_5	C_2H_5	H	H	H	H
121	CH_3	H	C_6H_5	H	H	H
122	CH_3	H	H	H	C_6H_5	H
123	H	CH_3	C_6H_5	H	H	H
124	H	CH_3	H	H	C_6H_5	H
125	CH_3	CH_3	H	C_6H_5	H	H
126	CH_3	CH_3	H	H	H	C_6H_5
127	H	H	H	H	H	$CH_2C_6H_5$
128	H	H	H	$CH_2C_6H_5$	H	H
129	$CH_2C_6H_5$	H	H	H	H	H
130	H	$CH_2C_6H_5$	H	H	H	H
131	CH_3	H	$CH_2C_6H_5$	H	H	H
132	CH_3	H	H	H	$CH_2C_6H_5$	H
133	H	CH_3	$CH_2C_6H_5$	H	H	H

LINKER NO.	R^{218}	R^{219}	R^{220}	R^{221}	R^{222}	R^{223}
134	H	CH_3	H	H	$CH_2C_6H_5$	H

The term "hydrido" denotes a single hydrogen atom (H) which may be attached, for example, to a carbon atom to form a hydrocarbyl group or attached to an oxygen atom to form an hydroxyl group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atomms. The term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl and cyclobutyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a fluoro atom within the group. Dihaloalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two fluoro atoms, such as difluoromethyl and difluorobutyl groups, or two chloro atoms, such as a dichloromethyl group, or one fluoro atom and one chloro atom, such as a fluoro-chloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl

groups. The term "difluoroalkyl" embraces alkyl groups having two fluoro atoms substituted on any one or two of the alkyl group carbon atoms. Preferably, when the difluoroalkyl group is attached at the triazole ring R^1 and R^2 positions of Formula I, the two fluoro atoms are substituted on the carbon atom which is attached directly to the triazole ring. Such preferred difluoroalkyl group may be characterized as an "alpha-carbon difluoro-substituted difluoroalkyl group" The terms "alkylol" and "hydroxyalkyl" embrace linear or branched alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond. The term "cycloalkenyl" embraces cyclic radicals having three to about ten ring carbon atoms including one or more double bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one to about ten carbon atoms attached to a divalent sulfur atom, such as a methythio group. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. The

term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "aryloxy" and "arylthio" denote radical respectively, aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes respectively divalent radicals SO and SO_2. The term "aralkoxy", alone or within another term, embraces an aryl group attached to an alkoxy group to form, for example, benzyloxy. The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. The term "heteroaryl" embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. Such heteroaryl may be attached as a substituent through a carbon atom of the heteroaryl ring system, or may be attached through a carbon atom of a moiety substituted on a heteroaryl ring-member carbon atom, for example, through the methylene substituent of imidazolemethyl moiety. Also, such heteroaryl may be attached through a ring nitrogen atom as long as aromaticity of the heteroaryl moiety is preserved after attachment.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a plurality or unsaturated bonds, with such plurality of bonds

either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

Conjugates of the invention formed from compounds of Formula I have been found to inhibit the action of angiotensin II in mammals. For example, specific biphenylmethyl 1H-substituted-imidazole compounds within Formula I have been evaluated for angiotensin II receptor binding and antihypertensive effects in renal hypertensive rats, as shown in EP #253,310 published 20 January 1988. Thus, conjugates of Formula I are therapeutically useful in methods for treating hypertension by administering to a hypertensive patient a therapeutically-effective amount of a conjugate containing a compound of Formula I, such that the conjugate is hydrolyzed by an enzyme found predominantly in the kidney so as to release an active angiotensin II antagonist species. The phrase "hypertensive patient" means, in this context, a mammalian subject suffering from the effects of hypertension or susceptible to a hypertensive condition if not treated to prevent or control such hypertension.

Included within the invention are conjugates of compounds of Formula I which are tautomeric forms of the described compounds, isomeric forms including diastereoisomers, and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and

phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicyclic, phenylacetic, mandelic, embonic (pamoic), methansulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic, cyclohexylaminosulfonic, stearic, algenic, β-hydroxy butyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I. Also, such pharmaceutical salts may be formed with either a compound of Formula I which is contained in the conjugate, or such salts may be formed with the conjugate itself.

Conjugates of the invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of

diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting conjugates with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active conjugates can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Conjugates of the invention may be prepared using precursors of highly active angiotensin II antagonists of Formula I. Examples of lesser active, suitable precursors are acid chloride, esters and amides of angiotensin II antagonists of Formula I. For example, ester precursors of angiotensin II antagonists, such as the methyl ester precursor made in Step 1 of Example 81, may be reacted with hydrazine to provide an amino terminal moiety which then can be reacted with a glutamic acid derivative to form a conjugate of the invention. Such precursors or intermediates themselves may be relatively strong, relatively weak, or inactive as AII antagonists. Also, conjugates of the invention may be prepared using angiotensin II antagonists lacking a reactive terminal amino moiety. Such angiotensin II antagonists, as shown in Example Nos. 78-80 of Table IV, lack a terminal amino moiety. These AII antagonist compounds may be modified as described in

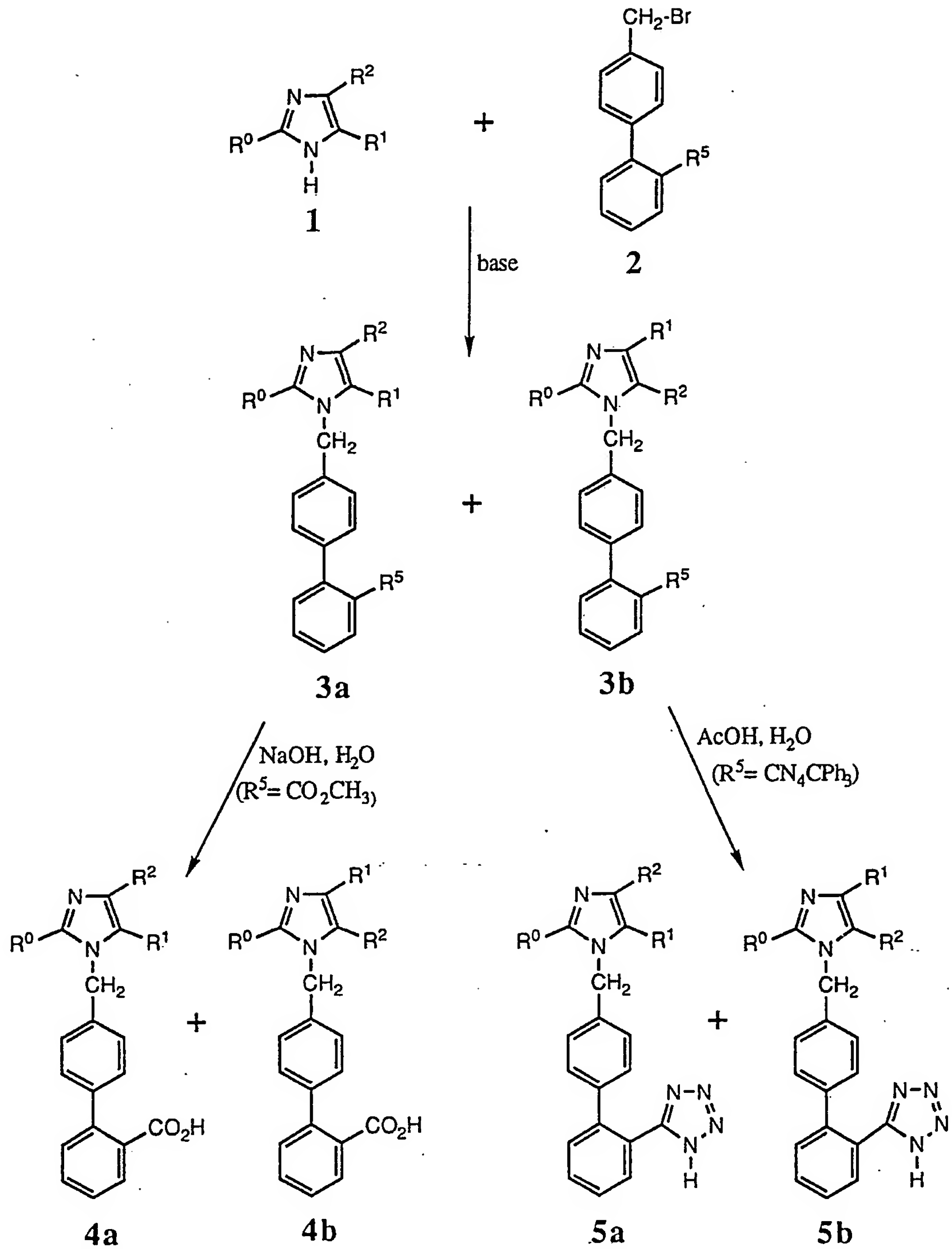
Example Nos. 711 and 712 to contain a terminal acid moiety which then may be connected to a glutamyl residue through a diamino-terminated linker group, such as shown in Tables I-III.

Synthetic Procedures

Conjugates of the invention are synthesized by reaction between precursors of the first and second residues. One of such precursors must contain a reactive acid moiety, and the other precursor must contain a reactive amino moiety, so that a conjugate is formed having a cleavable bond. Either precursor of the first and second residues may contain such reactive acid or amino moieties. Preferably, the precursors of the first residue are angiotensin II antagonists and will contain a reactive amino moiety or a moiety convertible to a reactive amino moiety. Inhibitor compounds lacking a reactive amino moiety may be chemically modified to provide such reactive amino moiety. Chemical modification of these inhibitor compounds lacking a reactive amino group may be accomplished by reacting an acid or an ester group on an AII antagonist compound with an amino compound having at least one reactive amino moiety. A suitable amino compound would be a diamino compound such as hydrazine, urea or ethylenediamine. Hydrazine, for example, may be reacted with a carboxylic acid or ester moiety of an AII antagonist compound to form a hydrazide derivative of such AII antagonist compound.

In the following general Synthetic Procedures, there is described firstly in Scheme I, methods for making suitable angiotensin II antagonists of Formula I for selection as the first component of the conjugate. Then, in Schemes II-VII, there are described general methods for making a conjugate by reacting a first component AII antagonist of Formula I with a cleavable second component represented by N-acetyl-γ-glutamic acid.

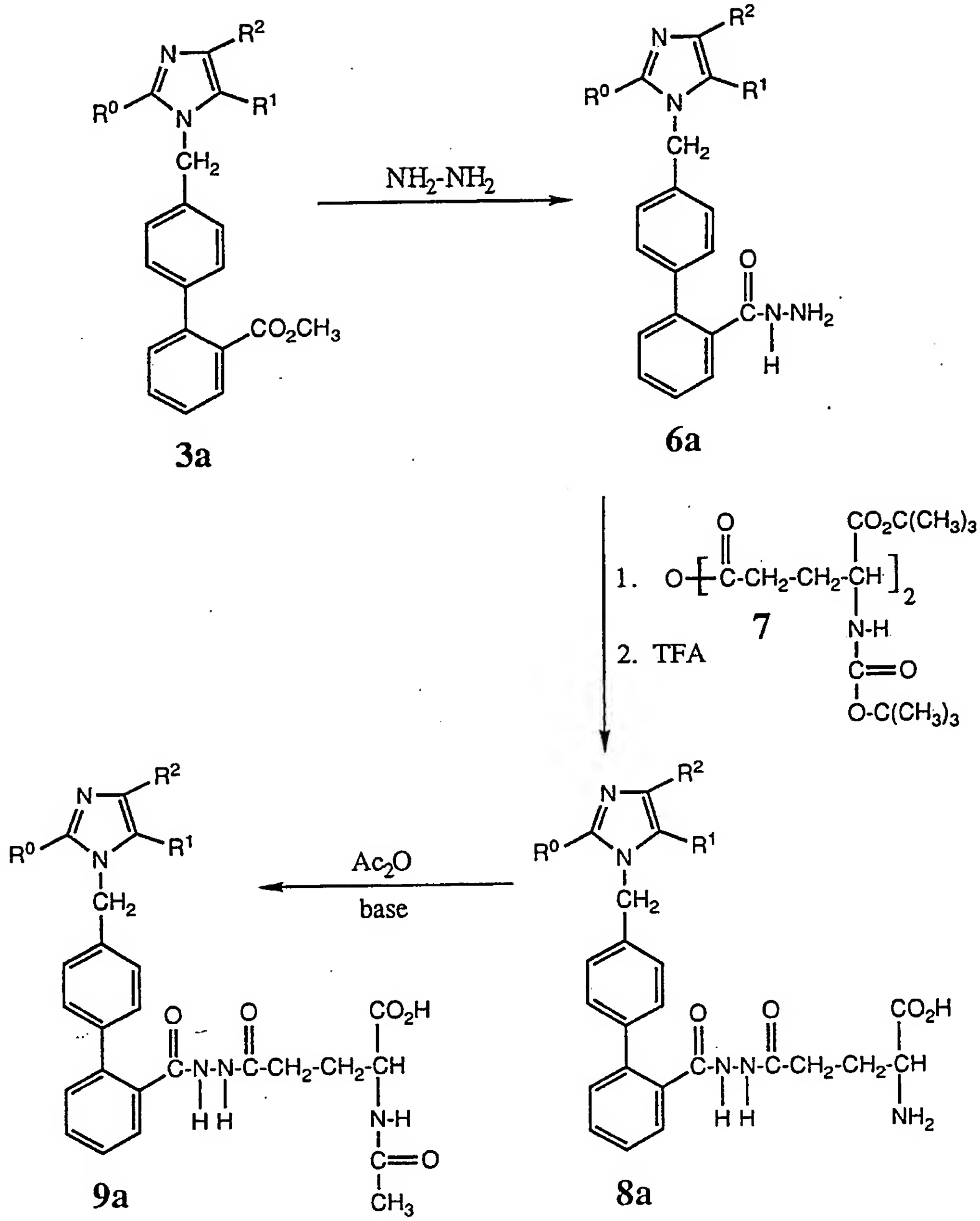
Scheme I



CH2-Br
R2
N
R0
R1
N
H
1
+
R5
base
2
3a
3b
NaOH, H2O
(R5= CO2CH3)
AcOH, H2O
(R5= CN4CPh3)
CO2H
4a
4b
5a
5b

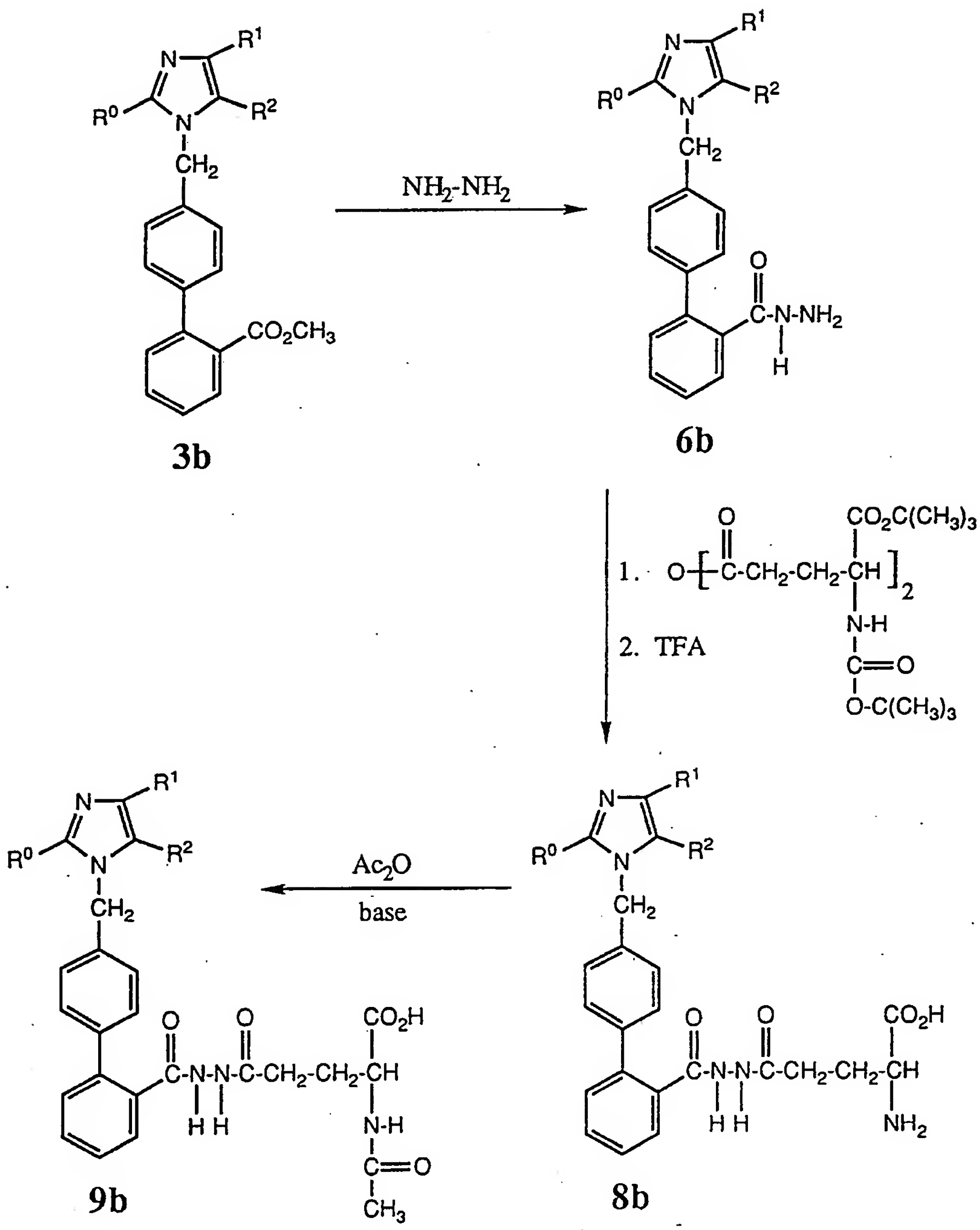
Synthetic Scheme I shows the coupling reaction of trisubstituted imidazoles 1 with the appropriate alkylating reagent 2. In the first step, 1 and 2 are reacted in dimethylformaide (DMF) in the presence of base, such as cesium carbonate, and a dehydrating agent, such as molecular seives, to give a mixture of coupled regioisomers 3a and 3b. The isomer mixture may be converted to mixtures of the corresponding acids 4a and 4b or tetrazoles 5a and 5b. Or, the isomers 3a and 3b may be separated by chromatographic methods, and each isomer may be reacted with the appropriate reagent to provide the acid- or tetrazole-substituted end product.

Scheme II



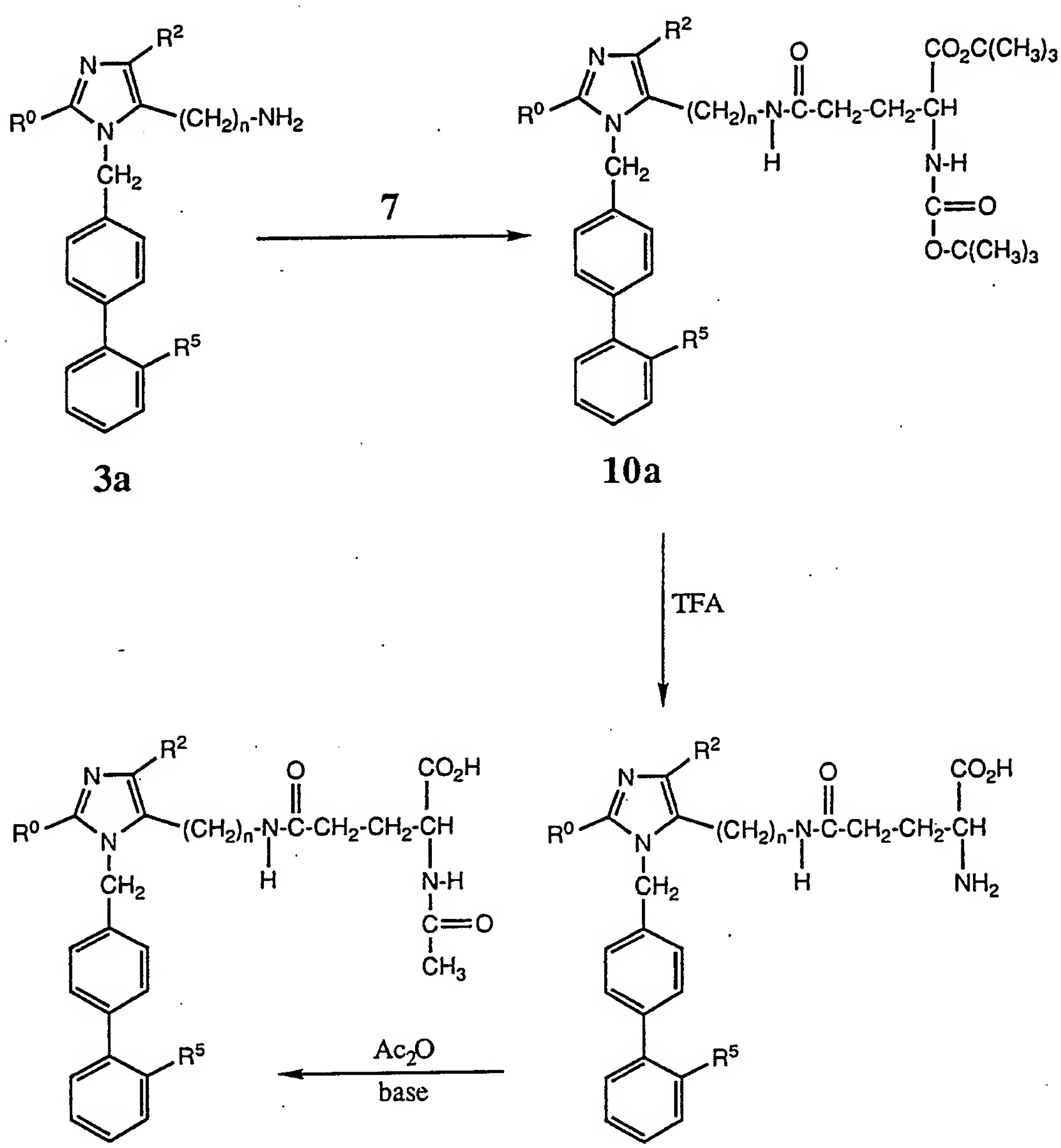
Synthetic Scheme II shows the preparation of the renal-selective angiotensin II antagonists by coupling γ-glutamic acid with one of the angiotensin II antagonist regiosiomers 3a (the synthesis of the other regioisomer is shown in Scheme III); the biphenyl R^5 acid moiety of the AII antagonist is coupled to the γ-acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3a is converted to the hydrazide 6a by the action of hydrazine. In step 2, the hydrazide 6a is first reacted with the symmetrical anhydride of the protected γ-glutamic acid 7 and subsequently reacted with trifluoroacetic acid (TFA) to give the deprotected coupled material 8a. In Step 3, the free amino group of 8a is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 9a.

Scheme III


NH2-NH2
3b
6b
1. O[C(=O)-CH2-CH2-CH(CO2C(CH3)3)(N-H-C(=O)-O-C(CH3)3)]2
2. TFA
Ac2O
base
9b
8b

Synthetic Scheme III shows the preparation of renal-selective angiotensin II antagonists by coupling γ-glutamic acid with one of the angiotensin II antagonist regioisomers 3b (the synthesis of the other regioisomer is shown in Scheme II); the biphenyl R^5 acid moiety of the AII antagonist is coupled to the γ-acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3b is converted to the hydrazide 6b by the action of hydrazine. In step 2, the hydrazide 6b is first reacted with the symmetrical anhydride of the protected γ-glutamic acid 7 and subsequently reacted with TFA to give the deprotected coupled material 8b. In step 3, the free amino group of 8b is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 9b.

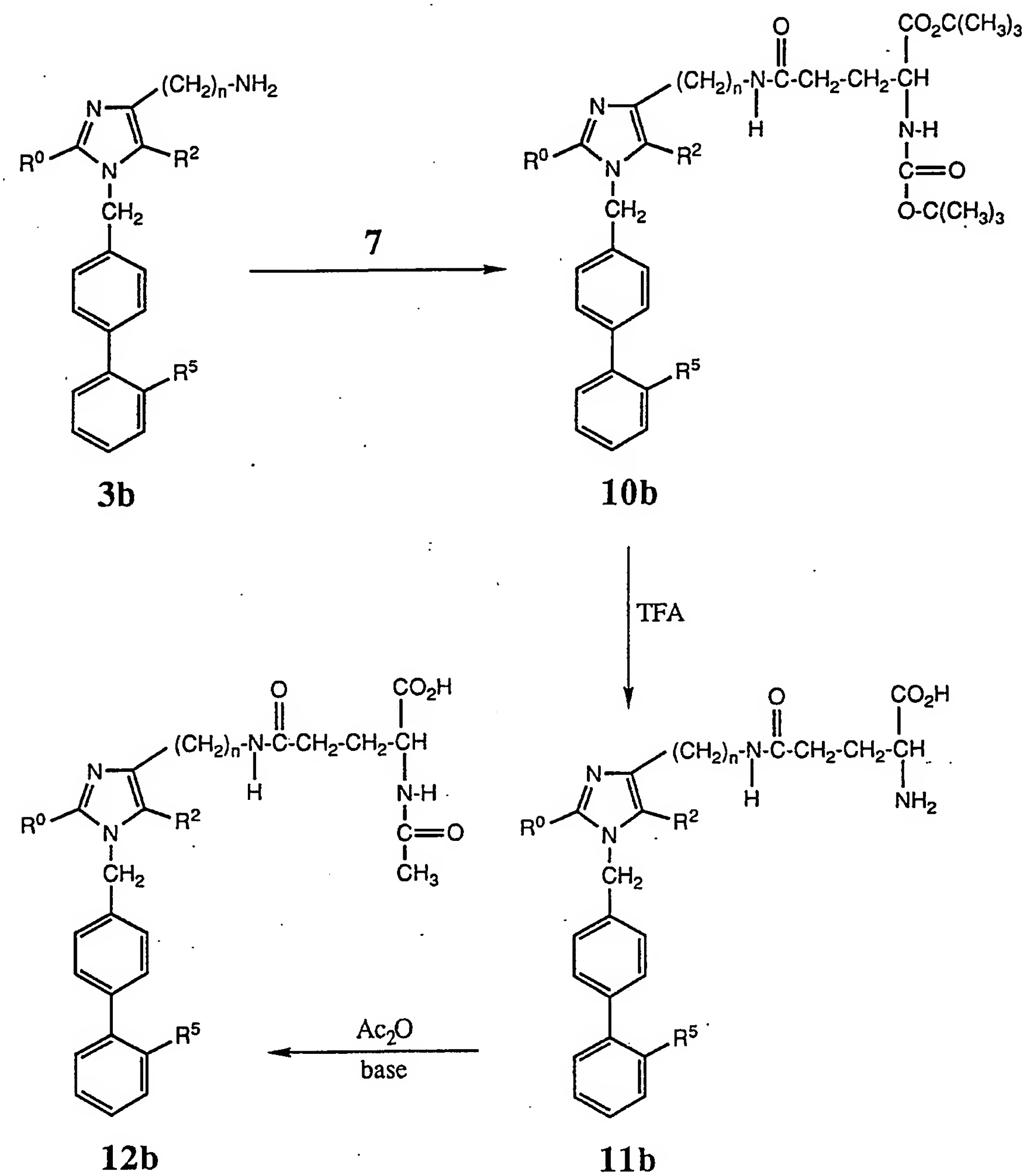
Scheme IV



3a 10a 11a 12a

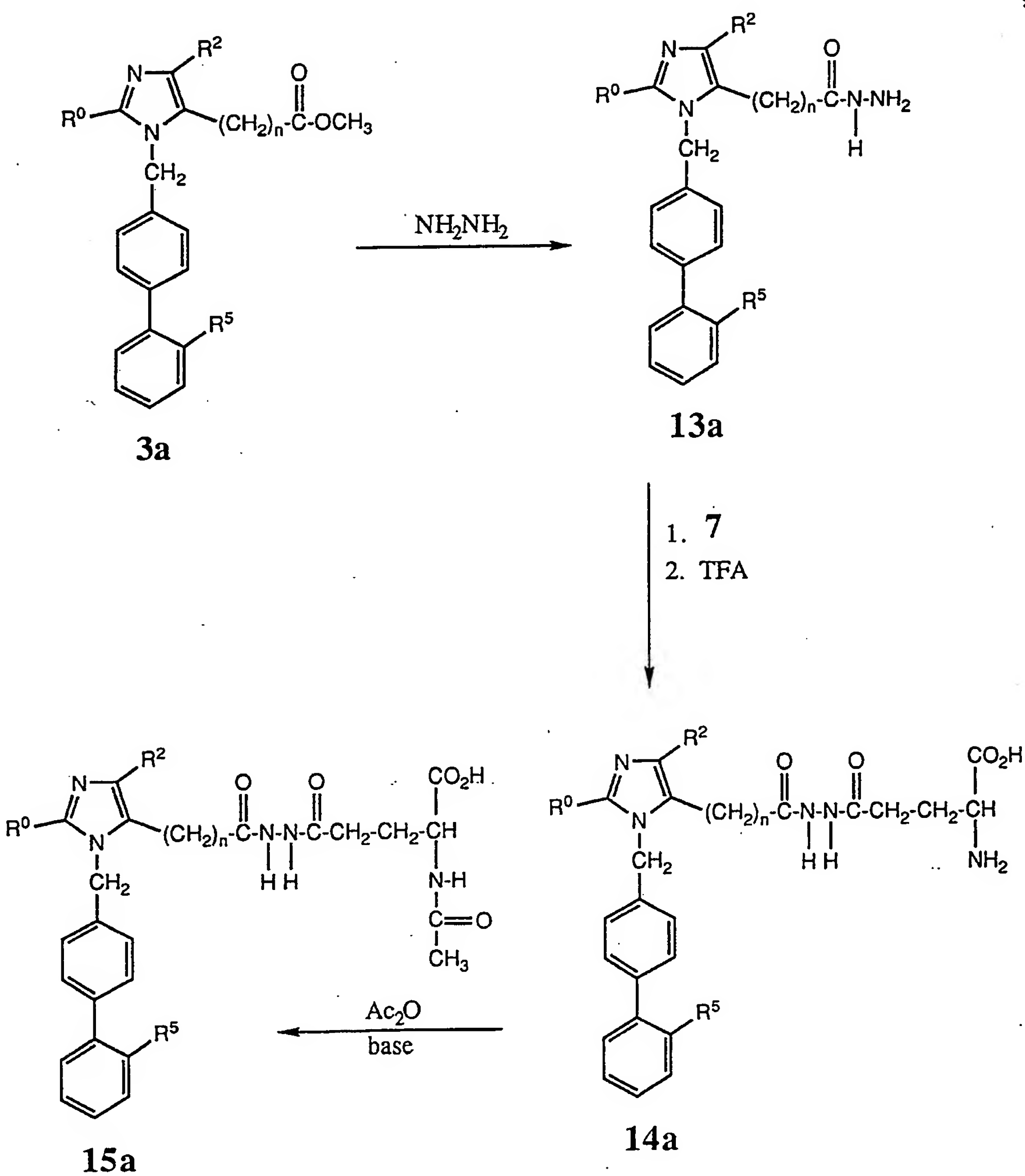
Synthetic Scheme IV shows the preparation of renal-selective angiotensin II antagonists by coupling γ-glutamic acid with one of the angiotensin II antagonist regiosiomers 3a which contains an amino moiety in the imidazole R^1 group (the synthesis of the other regioisomer is shown in Scheme V). In step 1, the AII antagonist 3a is reacted with the symmetrical anhydride of the protected γ-glutamic acid 7 to give 10a. In step 2, the protected material 10a is reacted with TFA to give the deprotected coupled material 11a. In step 3, the free amino compound 11a is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 12a.

Scheme V



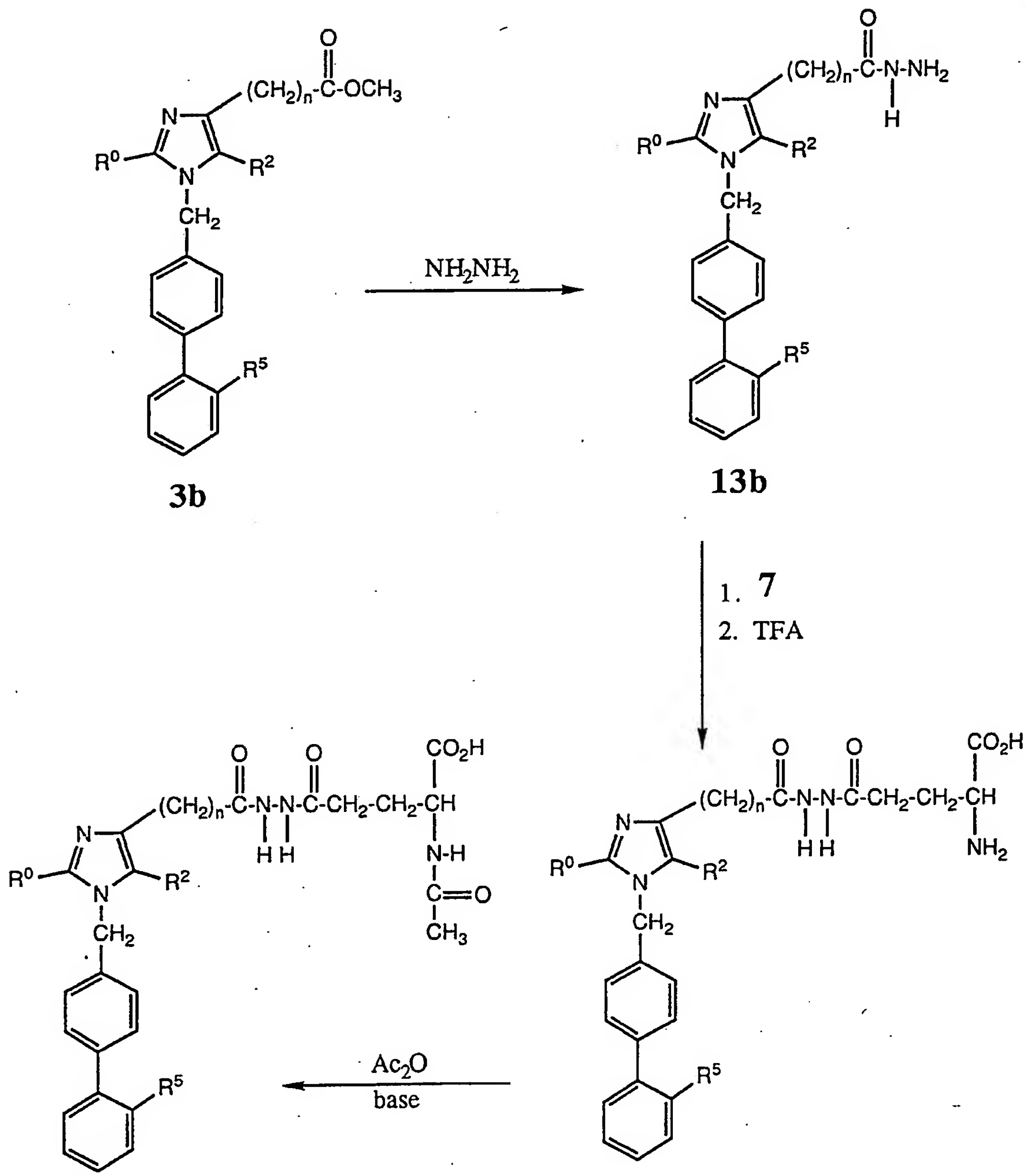
Synthetic Scheme V shows the preparation of renal-selective angiotensin II antagonists by coupling γ-glutamic acid with one of the angiotensin II antagonist regioisomers 3b which contains an amino moiety in the imidazole R^1 group (the synthesis of the other regioisomer is shown in Scheme IV). In step 1, the AII antagonist 3b is reacted with the symmetrical anhydride of the protected γ-glutamic acid 7 to give 10b. In step 2, the protected material 10b is reacted with TFA to give the deprotected coupled material 11b. In step 3, the free amino compound 11b is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 12b.

Scheme VI


R2
N
R0
N
(CH2)n-C-OCH3
O
CH2
R5
3a
NH2NH2
R2
N
R0
N
(CH2)n-C-N-NH2
O
H
CH2
R5
13a
1. 7
2. TFA
R2
N
R0
N
(CH2)n-C-N-N-C-CH2-CH2-CH
O
O
H H
CO2H
NH2
CH2
R5
14a
Ac2O
base
R2
N
R0
N
(CH2)n-C-N-N-C-CH2-CH2-CH
O
O
H H
CO2H
N-H
C=O
CH3
CH2
R5
15a

Synthetic Scheme VI shows the preparation of renal-selective angiotensin II antagonists by coupling γ-glutamic acid with one of the angiotensin II antagonist regioisomers 3a which contains an acid moiety in the imidazole R^1 group (the synthesis of the other regioisomer is shown in Scheme VII); the imidazole R^1 acid moiety of the AII antagonist is coupled to the γ-acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3a is converted to the hydrazide 13a by the action of hydrazine. In step 2, the hydrazide 13a is first reacted with the symmetrical anhydride of the protected γ-glutamic acid 7 and subsequently reacted with TFA to give the deprotected coupled material 14a. In step 3, the free amino group of 14a is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 15a.

Scheme VII



3b

13b

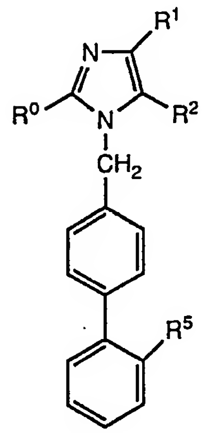
15b

14b

Synthetic Scheme VII shows the preparation of renal-selective angiotensin II antagonists by coupling γ-glutamic acid with one of the angiotensin II antagonist regioisomers 3b which contains an acid moiety in the imidazole R^1 group (the synthesis of the other isomer is shown in Scheme VII); the imidazole R^1 acid moiety of the AII antagonist is coupled to the γ-acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3b is converted to the hydrazide 13b by the action of hydrazine. In step 2, the hydrazide 13b is first reacted with the symmetrical anhydride of the protected γ-glutamic acid 7 and subsequently reacted with TFA to give the deprotected coupled material 14b. In step 3, the free amino group of 14b is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 15b.

The following Examples 1-80 shown in Table IV are angiotensin II antagonists suitable for selection as precursors to provide the first residue of a conjugate of the invention. These angiotensin II antagonists may be prepared generally by the procedures outlined above in Scheme I. Also, specific procedures for preparation of Examples 1-80 of Table IV may be found in EP #253,310 published 20 January 1988.

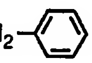
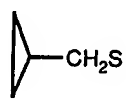
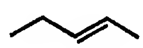
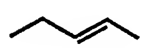
TABLE IV

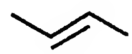
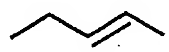
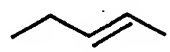
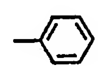


Ex. #	R^0	R^2	R^1	R^5
1	C_4H_9 (n)	CH_2OCOCH_3	Cl	CO_2H
2	C_4H_9 (n)	CH_2OH	NO_2	CO_2H
3	C_4H_9 (n)	CH_2OH	CF_3	CO_2H
4	SC_3H_7	CH_2OH	H	CO_2H
5	C_4H_9 (n)	CH_2OH	Cl	CO_2H
6	C_4H_9 (n)	Cl	CH_2OH	CO_2H

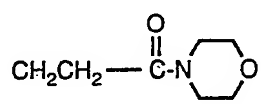
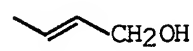
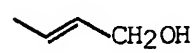
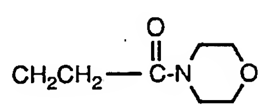
Ex. #	R^0	R^2	R^1	R^5
7	C_4H_9 (n)	H	CH_2OH	CO_2H
8	C_4H_9 (n)	CH_2OH	H	CO_2H
9	C_4H_9 (n)	CH_2OCH_3	Cl	CO_2H
10	C_4H_9 (n)	$CH_2OCH(CH_3)_2$	Cl	CO_2H
11	C_4H_9 (n)	CH_2OH	Br	CO_2H
12	C_4H_9 (n)	CH_2OH	F	CO_2H
13	C_4H_9 (n)	CH_2OH	I	CO_2H
14		CH_2OH	Cl	CO_2H
15		CH_2OH	Cl	CO_2H
16	C_4H_9 (n)	I	CH_2OH	CO_2H
17	C_3H_7 (n)	CH_2OH	Cl	CO_2H

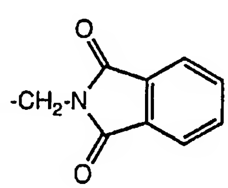
Ex. #	R^0	R^2	R^1	R^5
18	C_2H_5	CH_2OH	Cl	CO_2H
19	C_3H_7 (n)	CH_2OH	Cl	CO_2H
20	C_5H_{11} (n)	CH_2OH	Cl	CO_2H
21	C_6H_{13} (n)	CH_2OH	Cl	CO_2H
22	C_4H_9 (n)	CH_2SH	Cl	CO_2H
23	C_4H_9 (n)	$CH_2OC_6H_5$	Cl	CO_2H
24	C_3H_7 (n)	CHO	Cl	CO_2H
25	C_4H_9 (n)	CH_2CO_2H	Cl	CO_2H
26	C_4H_9 (n)	$CH(CH_3)CO_2H$	Cl	CO_2H
27	C_4H_9 (n)	NO_2	CH_2OH	CO_2H
28	C_4H_9 (n)	CH_2OCOCH_3	Cl	CO_2H

Ex. #	R^0	R^2	R^1	R^5
29	C_4H_9 (n)	$CH_2OCOCH_2CH_2$– 	Cl	CO_2H
30	SC_4H_9 (n)	CH_2OH	H	CO_2H
31		CH_2OH	H	CO_2H
32	C_4H_9 (n)	CHO	Cl	CO_2H
33	C_4H_9 (n)	CO_2CH_3	Cl	CO_2H
34	C_4H_9 (n)	$CONH_2$	Cl	CO_2H
35		CH_2OH	Cl	CO_2H
36		CHO	Cl	CO_2H
37	C_4H_9 (n)	CHO	H	CO_2H
38	C_4H_9 (n)	CHO	CF_3	CO_2H
39	C_4H_9 (n)	$CONHCH_3$	Cl	CO_2H

Ex. #	R^0	R^2	R^1	R^5
40	C_4H_9 (n)	$CON(CH_3)_2$	Cl	CO_2H
41		CH_2OH	Cl	CO_2H
42		CH_2OH	CF_3	CO_2H
43		CHO	Cl	CO2H
44	C_4H_9 (n)	$CH_2-N(H)-C(=O)-OC_2H_5$	Cl	CO_2H
45	C_4H_9 (n)	CH_2NHCO_2 	Cl	CO_2H
46	C_4H_9 (n)	$CH_2NHCO_2CH_3$	Cl	CO_2H
47	C_4H_9 (n)	$CH_2NHCO_2C_3H_7$	Cl	CO_2H
48	C_4H_9 (n)	$CH_2NHCO_2CH_2(CH_3)_2$	Cl	CO_2H

Ex. #	R^0	R^2	R^1	R^5
49	C_4H_9 (n)	$CH_2NHCO_2C_4H_9$	Cl	CO_2H
50	C_4H_9 (n)	CH_2-$NHCO_2$-adamantyl	Cl	CO_2H
51	C_3H_7 (n)	$CH_2NHCO_2CH_3$	Cl	CO_2H
52	C_4H_9 (n)	$CH_2NHCO_2CH_3$	Cl	CO_2H
53	C_4H_9 (n)	$CH_2NHCO_2C_2H_5$	Cl	CO_2H
54	C_4H_9 (n)	$CH_2NHCO_2C_3H_7$	Cl	CO_2H
55	C_4H_9 (n)	$CH_2NHCO_2C_4H_9$	Cl	CO_2H
56	C_4H_9 (n)	$CH_2NHCO_2CH(CH_3)_2$	Cl	CO_2H
57	C_4H_9 (n)	CH_2NHCO_2(1-naphthyl)	Cl	CO_2H
58	C_4H_9 (n)	$CH_2NHCONHCH_3$	Cl	CO_2H
59	C_4H_9 (n)	$CH_2NHCONHC_2H_5$	Cl	CO_2H

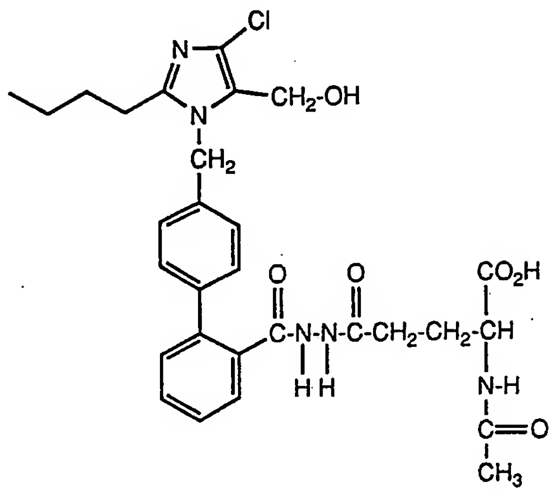
Ex. #	R^0	R^2	R^1	R^5
60	C_4H_9 (n)	$CH_2NHCONHC_3H_7$	Cl	CO_2H
61	C_4H_9 (n)	$CH_2NHCONHC_4H_9$	Cl	CO_2H
62	C_4H_9 (n)	$CH_2NHCONHCH(CH_3)_2$	Cl	CO_2H
63	C_4H_9 (n)	$CH_2NHCONH$(1-napthyl)	Cl	CO_2H
64	C_3H_7 (n)		H	CO_2H
65	C_3H_7 (n)		Cl	CO_2H
66	C_3H_7 (n)		Cl	CO_2H
67	C_4H_9 (n)		Cl	CO_2H
68	C_4H_9 (n)	$CH_2CH_2CO_2H$	Cl	CO_2H
69	C_4H_9 (n)	$CH_2CH_2CH_2CH_2CO_2H$	Cl	CO_2H

Ex. #	R^0	R^2	R^1	R^5
70		CH_2OH	Cl	CO_2H
71	C_4H_9 (n)	$-CH_2-O-C(=O)-N(H)-CH_3$	Cl	CO_2H
72	C_4H_9 (n)	$-CH_2-O-C(=S)-NHCH_3$	Cl	CO_2H
73	C_4H_9 (n)	$-CH_2N(H)-C(=S)-OC_3H_7$	H	CO_2H
74	C_4H_9 (n)	$-CH_2-O-C(=S)-NHCH_3$	H	CO_2H
75	C_4H_9 (n)	$-CH_2CH_2CH_2F$	Cl	CO_2H
76	C_4H_9 (n)	$-CH_2ONO_2$	Cl	CO_2H
77	C_4H_9 (n)	$-CH_2$ 	Cl	CO_2H

Ex. #	R^0	R^2	R^1	R^5
78	C_4H_9 (n)	CH_2OH	Cl	CN_4H
79	C_4H_9 (n)	Cl	CH_2OH	CN_4H
80	C_4H_9 (n)	CHO	Cl	CN_4H

A class of highly preferred specific conjugates of the invention is provided by conjugates formed from a biphenylmethyl 1H-substituted imidazole AII antagonist compound linked to a cleavable glutamyl residue. Each conjugate contains a diamino linker moiety which connects a terminal carboxylic acid moiety on the biphenylmethyl portion of the AII antagonist compound with a terminal carboxylic acid moiety on the gamma carbon of the cleavable glutamyl residue. Such conjugates are shown herein as Examples 81-146. General procedures for preparation of the conjugates of Examples 81-146 are described in Schemes II-III. Detailed procedures for preparation of representative conjugates are described in Examples 81 and 82. Similar procedures may be used for preparation of the conjugates identified as Examples 83-146 shown in Table V.

Example 81



N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide

Step 1: Preparation of 1-[(2'-methoxycarbonyl-biphenyl-4-yl)methyl]-2-butyl-4-chloro-5-hydroxymethylimidazole.

Under nitrogen, a solution of 6.69 g (36 mmol) of 2-butyl-4-chloro-5-hydroxymethylimidazole in 100 mL of anhydrous dimethylformamide (DMF) was treated with molecular seives and 11.0 g (36 mmol) of 4-bromomethyl-2'-methoxycarbonylbiphenyl. The reaction was allowed to stir at ambient temperature overnight and then was filtered. The DMF was removed in vacuo and the residue was partitioned between water and chloroform; the chloroform extracts were combined, dried ($MgSO_4$), and concentrated in vacuo giving 17.4 g of

crude material. Purification by silica gel chromatography (Waters Prep-500A) using ethyl acetate/hexane (40:60) gave the 4-hydroxymethyl isomer as the regioisomer with the lower R_f value and 6.27 g (42%) of the 5-hydroxymethyl isomer: NMR ($CDCl_3$) δ 0.91 (t, *J*=7Hz, 3H), 1.29-1.44 (m, 2H), 1.52 (t, *J*=8Hz, 1H), 1.63-1.76 (m, 2H), 2.62 (t, *J*=7Hz, 2H), 3.65 (s, 3H), 4.54 (d, *J*=8Hz, 2H), 7.02-7.08 (m, 2H), 7.25-7.36 (m, 3H), 7.38-7.47 (m, 1H), 7.50-7.58 (m, 1H), 7.83-7.90 (m, 1H).

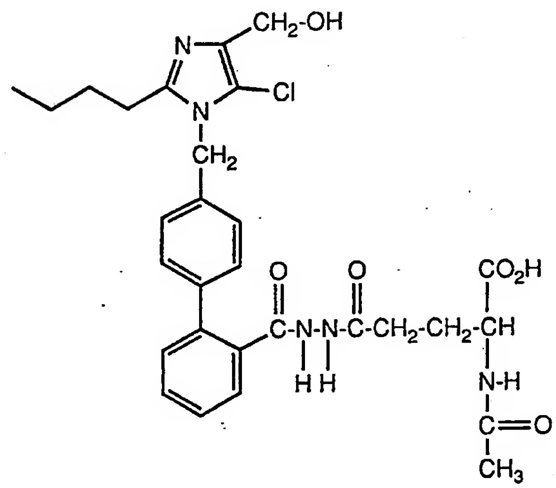
Step 2: Preparation of 1-[(2'-hydrazinylcarbonyl-biphenyl-4-yl)methyl]-2-butyl-4-chloro-5-hydroxymethylimidazole.

Under nitrogen, 6.27 g (15 mmol) of the 5-hydroxymethyl ester from step 1 was dissolved in 100 mL of methanol and trated with 15 mL (480 mmol) of anhydrous hydrazine. The reaction was allowed to stir at reflux overnight; concentration *in vacuo* gave 4.83 g of crude material. Purification by silica gel chromatography (Waters Prep-500A) using isopropanol/ethyl acetate (20:80) gave 4.27 g (68%) of the hydrazide as a colorless glass: NMR ($CDCl_3$) δ 0.81 (t, *J*=7Hz, 3H), 1.18-1.34 (m, 2H), 1.42-1.56 (m, 2H), 2.50 (t, *J*=Hz, 2H), 4.15-4.35 (br s, 2H), 4.35 (d, *J*=8Hz, 2H), 5.24 (t, *J*=8Hz, 1H), 7.05-7.13 (m, 2H), 7.32-7.44 (m, 5H), 7.45-7.54 (m, 1H), 9.34 (s, 1H).

Step 3: Preparation of N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

To a solution of 1.70 g (5.60 mmol) of N-Boc-L-glutamic acid-α-tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen was added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction was allowed to stir for 2 h and filtered under nitrogen. The anhydride solution was then added to a solution of 1.0 g (2.4 mmol) of hydrazide from step 2 in 75 mL of methylene chloride under nitrogen. The reaction was stirred overnight, concentrated to a volume of 25 mL, cooled to 0°C, and treated with 25 mL of TFA under nitrogen. The stirred reaction was allowed to warm to abmient temperature overnight and concentrated in vacuo. The crude product wad dissolved in 100 mL of acetonitrile/water (1:1) and the pH adjusted to 8 with 1 M K_2CO_3. The solution was cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K_2CO_3 was added every 30 min for 5 h; the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight. The pH was adjusted to 4 with 3 M HCl and the reaction was concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) using isocratic 25% acetonitrile/water (0.05% TFA) gave 1.0 g (75% overall yield from the hydrazide of step 2) of colorless product: NMR (DMSO-d_6) δ 0.81 (t, J=7Hz, 3H), 1.20-1.30 (m, 2H), 1.42-1.55 (m, 2H), 1.75-1.84 (m, 2H), 1.85 (s, 3H), 1.89-2.05 (m, 2H), 2.21 (t, J=7Hz, 2H), 4.13-4.24 (m, 1H), 4.35 (s, 2H), 7.05-7.12 (m, 2H), 7.37-7.58 (m, 6H), 8.12-8.17 (m, 2H); MS (FAB) m/e (rel. intensity) 584 (18), 568 (100), 225 (64); HRMS. Calcd for M+H: 584.2276. Found: 584.2240.

Example 82



N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide

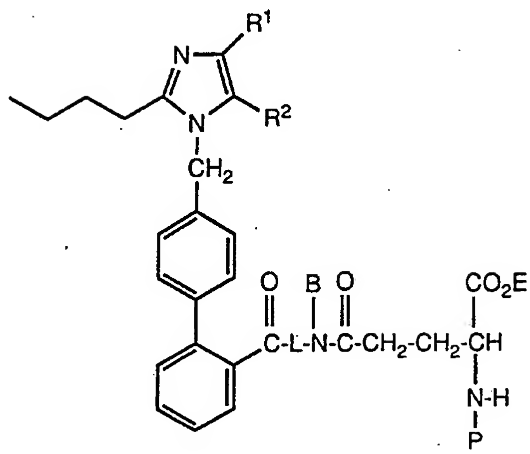
Step 1: Preparation of 1-[(2'-hydrazinylcarbonyl-biphenyl-4-yl)methyl]-2-butyl-5-chloro-4-hydroxymethylimidazole.

Under nitrogen, 4.13 g (10 mmol) of the 4-hydroxymethyl ester from step 1 of Example 81 is dissolved in 100 mL of methanol and is treated with 15 mL of (480 mmol) of anhydrous hydrazine. The reaction is allowed to stir at reflux overnight; concentration *in vacuo* gives the crude material. Purification by silica gel chromatography (Waters Prep-500A) gives the pure hydrazide.

Step 2: Preparation of N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide

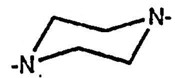
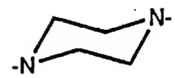
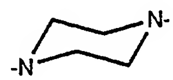
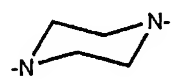
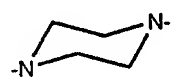
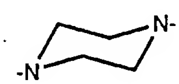
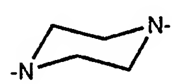
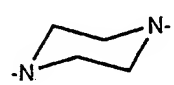
To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid-α-tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicylcohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.0 g (2.4 mmol) of the hydrazide from step 1 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K_2CO_3. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K_2CO_3 is added every 30 min for 5 h; the pH is mainained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) gives the product.

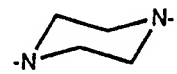
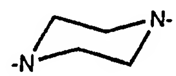
TABLE V



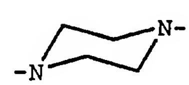
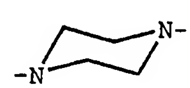
Ex. #	R^2	R^1	L	B	E	P
83	CH_2OH	Cl	-NH-	H	H	H
84	CH_2OH	Cl	-NH-	H	CH_3	H
85	CH_2OH	Cl	-NH-	H	CH_3	$COCH_3$
86	CH_2OH	Cl	-NH-	H	C_2H_5	$COCH_3$
87	CH_2OH	Cl	-NH-	H	C_2H_5	H
88	CH_2OH	Cl	-NH-	H	H	$COCH_2Cl$
89	CH_2OH	Cl	-NH-	H	H	COC_4H_9 (n)

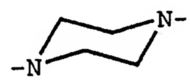
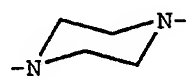
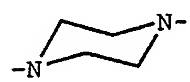
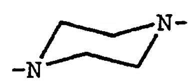
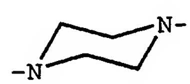
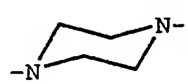
Ex. #	R^2	R^1	L	B	E	P
90	Cl	CH_2OH	-NH-	H	H	H
91	CH_2OH	Cl	$-NHCH_2CH_2-$	H	H	$COCH_3$
92	CH_2OH	Cl	$-NHCH_2CH_2-$	H	H	H
93	CH_2OH	Cl	$-NHCH_2CH_2-$	H	CH_3	H
94	CH_2OH	Cl	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
95	CH_2OH	Cl	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
96	CH_2OH	Cl	$-NHCH_2CH_2-$	H	C_2H_5	H
97	CH_2OH	Cl	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
98	CH_2OH	Cl	$-NHCH_2CH_2-$	H	H	COC_4H_9 (n)
99	Cl	CH_2OH	$-NHCH_2CH_2-$	H	H	$COCH_3$
100	Cl	CH_2OH	$-NHCH_2CH_2-$	H	H	H

Ex. #	R^2	R^1	L	B	E	P
101	CH_2OH	Cl		*	H	$COCH_3$
102	CH_2OH	Cl		*	H	H
103	CH_2OH	Cl		*	CH_3	H
104	CH_2OH	Cl		*	CH_3	$COCH_3$
105	CH_2OH	Cl		*	C_2H_5	$COCH_3$
106	CH_2OH	Cl		*	C_2H_5	H
107	CH_2OH	Cl		*	H	COC_4H_9(n))
108	CH_2OH	Cl		*	H	COC_4H_9(n))

Ex. #	R^2	R^1	L	B	E	P
109	Cl	CH_2OH		*	H	$COCH_3$
110	Cl	CH_2OH		*	H	H
111	CH_2OCH_3	Cl	-NH-	H	H	$COCH_3$
112	CH_2OCH_3	Cl	-NH-	H	H	H
113	Cl	CH_2OCH_3	-NH-	H	H	$COCH_3$
114	Cl	CH_2OCH_3	-NH-	H	H	H
115	CH_2OH	CF_3	-NH-	H	H	$COCH_3$
116	CH_2OH	CF_3	-NH-	H	H	H
117	CH_2OH	C_2F_5	-NH-	H	H	$COCH_3$
118	CH_2OH	C_2F_5	-NH-	H	H	H
119	CH_2OH	C_3F_7	-NH-	H	H	$COCH_3$

Ex. #	R^2	R^1	L	B	E	P
120	CH_2OH	C_3F_7	-NH-	H	H	H
121	CHO	Cl	-NH-	H	H	$COCH_3$
122	CHO	Cl	-NH-	H	H	H
123	Cl	CHO	-NH-	H	H	$COCH_3$
124	Cl	CHO	-NH-	H	H	H
125	CO_2H	Cl	-NH-	H	H	$COCH_3$
126	CO_2H	Cl	-NH-	H	H	$COCH_3$
127	Cl	CO_2H	-NH-	H	H	$COCH_3$
128	Cl	CO_2H	-NH-	H	H	H
129	CH_2OH	Br	-NH-	H	H	$COCH_3$
130	CH_2OH	Br	-NH-	H	H	H

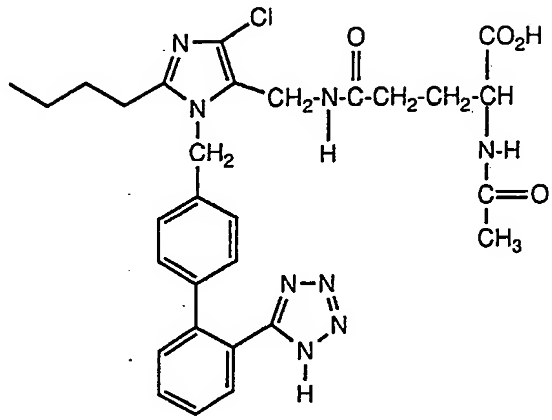
Ex. #	R^2	R^1	L	B	E	P
131	Cl	CHO	$-NHCH_2CH_2-$	H	H	$COCH_3$
132	Cl	CHO	$-NHCH_2CH_2-$	H	H	H
133	CO_2H	Cl	$-NHCH_2CH_2-$	H	H	$COCH_3$
134	CO_2H	Cl	$-NHCH_2CH_2-$	H	H	H
135	Cl	CO_2H	$-NHCH_2CH_2-$	H	H	$COCH_3$
136	Cl	CO_2H	$-NHCH_2CH_2-$	H	H	H
137	CH_2OH	Br	$-NHCH_2CH_2-$	H	H	$COCH_3$
138	CH_2OH	Br	$-NHCH_2CH_2-$	H	H	H
139	Cl	CHO		*	H	$COCH_3$
140	Cl	CHO		*	H	H

Ex. #	R^2	R^1	L	B	E	P
141	CO_2H	Cl		*	H	$COCH_3$
142	CO_2H	Cl		*	H	H
143	Cl	CO_2H		*	H	$COCH_3$
144	Cl	CO_2H		*	H	H
145	CH_2OH	Br		*	H	$COCH_3$
146	CH_2OH	Br		*	H	H

* B | -L-N- equals piperazinyl

Another class of highly preferred specific conjugates of the invention is provided by conjugates formed from a biphenylmethyl 1H-substituted imidazole AII antagonist compound having a terminal amino group attached to the imidazole nucleus. In this family of conjugates, the cleavable glutamyl residue is attached through an amide bond formed between the carbonyl at the gamma carbon of the glutamyl residue and the terminal amino nitrogen of the AII antagonist imidazole nucleus. Such conjugates are shown as Examples #147-#710. General procedures for preparation of the conjugates of Examples #147-#710 are described in Schemes IV-V. Detailed procedures for preparation of representative conjugates are described in Examples #147 and #148. Procedures similar to these aforementioned general and specific procedures may be used for preparation of the conjugates identified as Examples #149-#710 shown in Table VI.

Example 147



N2-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine

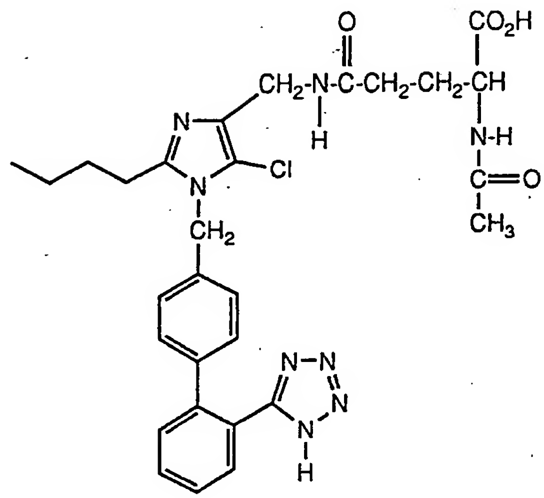
Step 1: Preparation of 5-aminomethyl-2-butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

A solution of 4.20 g (10 mmol) of the compound of Example 80, 7.7 g (100 mmol) of ammonium acetate, and 439 mg (7 mmol) of $NaBH_3CN$ in 30 mL of absolute methanol is stirred at ambient temperature for 48 h. Concentrated HCl is added until pH<2, and the methanol is removed in vacuo. The residue is dissolved in water and is extracted with ethyl acetate. The aqueous solution is brought to pH>10 with 50% NaOH, is saturated with NaCl, and is extracted with methylene chloride. The extracts are combined, are dried ($MgSO_4$), and are evaporated in vacuo to give the crude product. Purification by reverse phase chromatography (Waters DeltaPrep-3000) provides the pure 5-aminomethyl product.

Step 2: Preparation of N2-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine

To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid-α-tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicylcohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of the 5-aminomethyl compound of step 1 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated *in vacuo*. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K_2CO_3. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K_2CO_3 is added every 30 min for 5 h; the pH is mainained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Delta- prep-3000) gives the pure product.

Example 148



N2-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine

Step 1: Preparation of 2-butyl-5-chloro-4-formyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

A mixture of 2.11 g (5.0 mmol) of the compound of Example 79 and 3.08 g (35 mmol) of activated manganese dioxide in 30 mL of methylene chloride at ambient temperature is stirred for 40 h. The reaction mixture is filtered through celite, and the filtrate is concentrated in vacuo. Purification by reverse phase chromatography provided the pure 4-formyl product.

Step 2: Preparation of 4-aminomethyl-2-butyl-5-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

A solution of 4.20 g (10 mmol) of the aldehyde from step 1, 7.7 g (100 mmol) of ammonium acetate, and 439

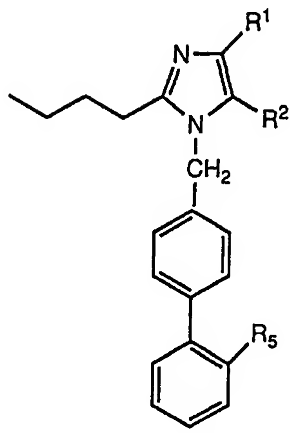
mg (7 mmol) of $NaBH_3CN$ in 30 mL of absolute methanol is stirred at ambient temperature for 48 h. Concentrated HCl is added until pH<2, and the methanol is removed in vacuo. The residue is dissolved in water and is extracted with ethyl acetate. The aqueous solution is brought to pH>10 with 50% NaOH, is saturated with NaCl, and is extracted with methylene chloride. The extracts are combined, are dried ($MgSO_4$), and are evaporated in vacuo to give the crude product. Purification by reverse phase chromatography (Waters Deltaprep-3000) provides the pure product.

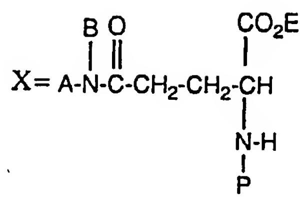
Step 3: Preparation of N2-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine

To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid-α-tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicylcohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of the 4-aminomethyl compound of step 2 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K_2CO_3. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K_2CO_3 is added every 30 min for 5 h; the pH is mainained at 9 and the reaction temperature is kept below

5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Delta-prep-3000) gives the pure product.

TABLE VI





Ex: #	R^1	R^2	R_5	A	B	E	P
149	Cl	X	CO_2H	single bond	H	H	$COCH_3$
150	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
151	Cl	X	CO_2H	single bond	H	H	COC_4H_9
152	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
153	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
154	Cl	X	CN_4H	single bond	H	H	$COCH_3$

Ex: #	R^1	R^2	R_5	A	B	E	P
155	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
156	Cl	X	CN_4H	single bond	H	H	COC_4H_9
157	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
158	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
159	Cl	X	CO_2H	single bond	H	H	H
160	Cl	X	CO_2H	single bond	H	CH_3	H
161	Cl	X	CO_2H	single bond	H	C_2H_5	H
162	Cl	X	CN_4H	single bond	H	H	H
163	Cl	X	CN_4H	single bond	H	CH_3	H
164	Cl	X	CN_4H	single bond	H	C_2H_5	H
165	Cl	X	CO_2H	$-CH_2-$	H	H	$COCH_3$
166	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$

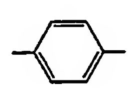
Ex: #	R^1	R^2	R_5	A	B	E	P
167	Cl	X	CO_2H	single bond	H	H	COC_4H_9
168	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
169	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
170	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
171	Cl	X	CN_4H	single bond	H	H	COC_4H_9
172	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
173	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
174	Cl	X	CO_2H	$-CH_2-$	H	H	H
175	Cl	X	CO_2H	single bond	H	CH_3	H
176	Cl	X	CO_2H	single bond	H	C_2H_5	H
177	Cl	X	CN_4H	$-CH_2-$	H	H	H

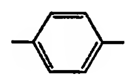
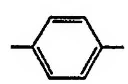
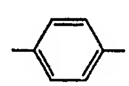
Ex: #	R^1	R^2	R_5	A	B	E	P
178	Cl	X	CN_4H	single bond	H	CH_3	H
179	Cl	X	CN_4H	single bond	H	C_2H_5	H
180	Cl	X	CN_4H	$-CH_2-$	CH_3	H	H
181	Cl	X	CN_4H	$-CH_2-$	CH_3	H	$COCH_3$
182	Cl	X	CO_2H	$-CH_2CH_2-$	H	H	$COCH_3$
183	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
184	Cl	X	CO_2H	single bond	H	H	COC_4H_9
185	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
186	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
187	Cl	X	CN_4H	$-CH_2CH_2-$	H	H	$COCH_3$
188	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$

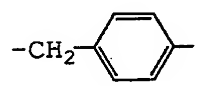
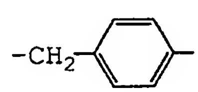
Ex: #	R^1	R^2	R_5	A	B	E	P
189	Cl	X	CN_4H	single bond	H	H	COC_4H_9
190	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
191	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
192	Cl	X	CO_2H	$-CH_2CH_2-$	H	H	H
193	Cl	X	CO_2H	single bond	H	CH_3	H
194	Cl	X	CO_2H	single bond	H	C_2H_5	H
195	Cl	X	CN_4H	$-CH_2CH_2-$	H	H	H
196	Cl	X	CN_4H	single bond	H	CH_3	H
197	Cl	X	CN_4H	single bond	H	C_2H_5	H
198	Cl	X	CO_2H	C_3H_6 (n)	H	H	$COCH_3$
199	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$

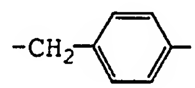
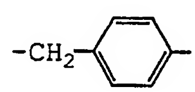
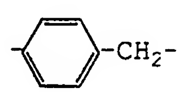
Ex: #	R^1	R^2	R_5	A	B	E	P
200	Cl	X	CO_2H	single bond	H	H	COC_4H_9
201	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
202	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
203	Cl	X	CN_4H	C_3H_6 (n)	H	H	$COCH_3$
204	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
205	Cl	X	CN_4H	single bond	H	H	COC_4H_9
206	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
207	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
208	Cl	X	CO_2H	C_3H_6 (n)	H	H	H
209	Cl	X	CO_2H	single bond	H	CH_3	H
210	Cl	X	CO_2H	single bond	H	C_2H_5	H

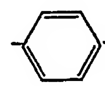
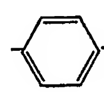
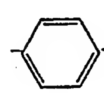
Ex: #	R^1	R^2	R_5	A	B	E	P
211	Cl	X	CN_4H	C_3H_6 (n)	H	H	H
212	Cl	X	CN_4H	single bond	H	CH_3	H
213	Cl	X	CN_4H	single bond	H	C_2H_5	H
214	Cl	X	CO_2H	C_4H_8 (n)	H	H	$COCH_3$
215	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
216	Cl	X	CO_2H	single bond	H	H	COC_4H_9
217	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
218	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
219	Cl	X	CN_4H	C_4H_8 (n)	H	H	$COCH_3$
220	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
221	Cl	X	CN_4H	single bond	H	H	COC_4H_9

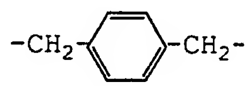
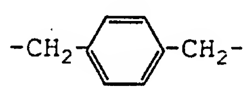
Ex: #	R^1	R^2	R_5	A	B	E	P
222	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
223	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
224	Cl	X	CO_2H	C_4H_8 (n)	H	H	H
225	Cl	X	CO_2H	single bond	H	CH_3	H
226	Cl	X	CO_2H	single bond	H	C_2H_5	H
227	Cl	X	CN_4H	C_4H_8 (n)	H	H	H
228	Cl	X	CN_4H	single bond	H	CH_3	H
229	Cl	X	CN_4H	single bond	H	C_2H_5	H
230	Cl	X	CO_2H		H	H	$COCH_3$
231	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
232	Cl	X	CO_2H	single bond	H	H	COC_4H_9

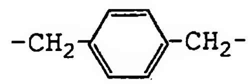
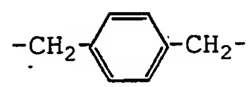
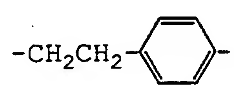
Ex: #	R^1	R^2	R_5	A	B	E	P
233	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
234	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
235	Cl	X	CN_4H		H	H	$COCH_3$
236	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
237	Cl	X	CN_4H	single bond	H	H	COC_4H_9
238	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
239	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
240	Cl	X	CO_2H		H	H	H
241	Cl	X	CO_2H	single bond	H	CH_3	H
242	Cl	X	CO_2H	single bond	H	C_2H_5	H
243	Cl	X	CN_4H		H	H	H

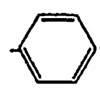
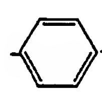
Ex: #	R^1	R^2	R_5	A	B	E	P
244	Cl	X	CN_4H	single bond	H	CH_3	H
245	Cl	X	CN_4H	single bond	H	C_2H_5	H
246	Cl	X	CO_2H		H	H	$COCH_3$
247	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
248	Cl	X	CO_2H	single bond	H	H	COC_4H_9
249	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
250	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
251	Cl	X	CN_4H		H	H	$COCH_3$
252	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
253	Cl	X	CN_4H	single bond	H	H	COC_4H_9
254	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$

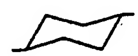
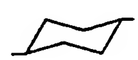
Ex: #	R^1	R^2	R_5	A	B	E	P
255	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
256	Cl	X	CO_2H		H	H	H
257	Cl	X	CO_2H	single bond	H	CH_3	H
258	Cl	X	CO_2H	single bond	H	C_2H_5	H
259	Cl	X	CN_4H		H	H	H
260	Cl	X	CN_4H	single bond	H	CH_3	H
261	Cl	X	CN_4H	single bond	H	C_2H_5	H
262	Cl	X	CO_2H		H	H	$COCH_3$
263	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
264	Cl	X	CO_2H	single bond	H	H	COC_4H_9

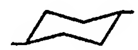
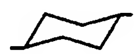
Ex: #	R^1	R^2	R_5	A	B	E	P
265	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
266	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
267	Cl	X	CN_4H	 $-CH_2-$	H	H	$COCH_3$
268	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
269	Cl	X	CN_4H	single bond	H	H	COC_4H_9
270	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
271	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
272	Cl	X	CO_2H	 $-CH_2-$	H	H	H
273	Cl	X	CO_2H	single bond	H	CH_3	H
274	Cl	X	CO_2H	single bond	H	C_2H_5	H
275	Cl	X	CN_4H	 $-CH_2-$	H	H	H

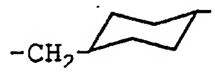
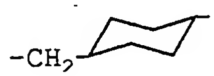
Ex: #	R^1	R^2	R_5	A	B	E	P
276	Cl	X	CN_4H	single bond	H	CH_3	H
277	Cl	X	CN_4H	single bond	H	C_2H_5	H
278	Cl	X	CO_2H		H	H	$COCH_3$
279	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
280	Cl	X	CO_2H	single bond	H	H	COC_4H_9
281	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
282	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
283	Cl	X	CN_4H		H	H	$COCH_3$
284	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
285	Cl	X	CN_4H	single bond	H	H	COC_4H_9
286	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$

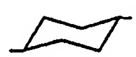
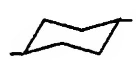
Ex: #	R^1	R^2	R_5	A	B	E	P
287	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
288	Cl	X	CO_2H		H	H	H
289	Cl	X	CO_2H	single bond	H	CH_3	H
290	Cl	X	CO_2H	single bond	H	C_2H_5	H
291	Cl	X	CN_4H		H	H	H
292	Cl	X	CN_4H	single bond	H	CH_3	H
293	Cl	X	CN_4H	single bond	H	C_2H_5	H
294	Cl	X	CN_4H		H	H	$COCH_3$
295	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
296	Cl	X	CO_2H	single bond	H	H	COC_4H_9
297	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$

Ex: #	R^1	R^2	R_5	A	B	E	P
298	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
299	Cl	X	CN_4H	$-CH_2CH_2-$	H	H	H
300	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
301	Cl	X	CN_4H	single bond	H	COC_4H_9	
302	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
303	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
304	Cl	X	CN_4H	$-CH_2-CH_2-$	H	H	$COCH_3$
305	Cl	X	CO_2H	single bond	H	CH_3	H
306	Cl	X	CO_2H	single bond	H	C_2H_5	H
307	Cl	X	CN_4H	$-CH_2-CH_2-$	H	H	H

Ex: #	R^1	R^2	R_5	A	B	E	P
308	Cl	X	CN_4H	single bond	H	CH_3	H
309	Cl	X	CN_4H	single bond	H	C_2H_5	H
310	Cl	X	CO_2H		H	H	$COCH_3$
311	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
312	Cl	X	CO_2H	single bond	H	H	COC_4H_9
313	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
314	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
315	Cl	X	CN_4H		H	H	$COCH_3$
316	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
317	Cl	X	CN_4H	single bond	H	H	COC_4H_9
318	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$

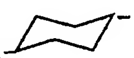
Ex: #	R^1	R^2	R_5	A	B	E	P
319	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
320	Cl	X	CO_2H		H	H	H
321	Cl	X	CO_2H	single bond	H	CH_3	H
322	Cl	X	CO_2H	single bond	H	C_2H_5	H
323	Cl	X	CN_4H		H	H	H
324	Cl	X	CN_4H	single bond	H	CH_3	H
325	Cl	X	CN_4H	single bond	H	C_2H_5	H
326	Cl	X	CO_2H	$-CH_2-$ 	H	H	$COCH_3$
327	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
328	Cl	X	CO_2H	single bond	H	H	COC_4H_9
329	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$

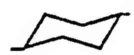
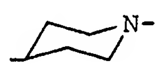
Ex: #	R^1	R^2	R_5	A	B	E	P
330	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
331	Cl	X	CN_4H		H	H	$COCH_3$
332	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
333	Cl	X	CN_4H	single bond	H	H	COC_4H_9
334	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
335	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
336	Cl	X	CO_2H		H	H	H
337	Cl	X	CO_2H	single bond	H	CH_3	H
338	Cl	X	CO_2H	single bond	H	C_2H_5	H
339	Cl	X	CN_4H		H	H	H
340	Cl	X	CN_4H	single bond	H	CH_3	H

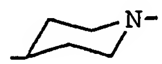
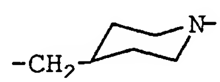
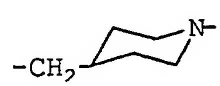
Ex: #	R^1	R^2	R_5	A	B	E	P
341	Cl	X	CN_4H	single bond	H	C_2H_5	H
342	Cl	X	CO_2H	$-CH_2-$	H	H	$COCH_3$
343	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
344	Cl	X	CO_2H	single bond	H	H	COC_4H_9
345	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
346	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
347	Cl	X	CN_4H	$-CH_2-$	H	H	$COCH_3$
348	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
349	Cl	X	CN_4H	single bond	H	H	COC_4H_9
350	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
351	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$

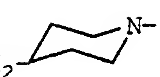
Ex: #	R^1	R^2	R_5	A	B	E	P
352	Cl	X	CO_2H		H	H	H
353	Cl	X	CO_2H	single bond	H	CH_3	H
354	Cl	X	CO_2H	single bond	H	C_2H_5	H
355	Cl	X	CN_4H		H	H	H
356	Cl	X	CN_4H	single bond	H	CH_3	H
357	Cl	X	CN_4H	single bond	H	C_2H_5	H
358	Cl	X	CO_2H		H	H	$COCH_3$
359	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
360	Cl	X	CO_2H	single bond	H	H	COC_4H_9
361	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
362	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$

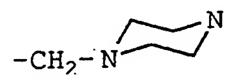
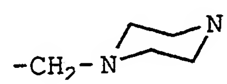
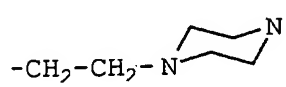
Ex: #	R^1	R^2	R_5	A	B	E	P
363	Cl	X	CN_4H		H	H	$COCH_3$
364	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
365	Cl	X	CN_4H	single bond	H	H	COC_4H_9
366	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
367	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
368	Cl	X	CO_2H		H	H	H
369	Cl	X	CO_2H	single bond	H	CH_3	H
370	Cl	X	CO_2H	single bond	H	C_2H_5	H
371	Cl	X	CN_4H		H	H	H
372	Cl	X	CN_4H	single bond	H	CH_3	H

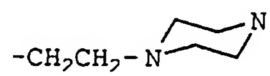
Ex: #	R^1	R^2	R_5	A	B	E	P
373	Cl	X	CN_4H	single bond	H	C_2H_5	H
374	Cl	X	CN_4H	$-CH_2CH_2-$ 	H	H	$COCH_3$
375	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
376	Cl	X	CO_2H	single bond	H	H	COC_4H_9
377	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
378	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
379	Cl	X	CN_4H	$-CH_2CH_2-$ 	H	H	H
380	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
381	Cl	X	CN_4H	single bond	H	H	COC_4H_9
382	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
383	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$

Ex: #	R^1	R^2	R_5	A	B	E	P
384	Cl	X	CN_4H	 $-CH_2CH_2-$	H	H	$COCH_3$
385	Cl	X	CO_2H	single bond	H	CH_3	H
386	Cl	X	CO_2H	single bond	H	C_2H_5	H
387	Cl	X	CN_4H	 $-CH_2CH_2-$	H	H	H
388	Cl	X	CN_4H	single bond	H	CH_3	H
389	Cl	X	CN_4H	single bond	H	C_2H_5	H
390	Cl	X	CN_4H		*	H	$COCH_3$
391	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
392	Cl	X	CO_2H	single bond	H	H	COC_4H_9
393	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
394	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$

Ex: #	R^1	R^2	R_5	A	B	E	P
395	Cl	X	CN_4H		*	H	H
396	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
397	Cl	X	CN_4H	single bond	H	H	COC_4H_9
398	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
399	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
400	Cl	X	CN_4H		*	H	$COCH_3$
401	Cl	X	CO_2H	single bond	H	CH_3	H
402	Cl	X	CO_2H	single bond	H	C_2H_5	H
403	Cl	X	CN_4H		*	H	H
404	Cl	X	CN_4H	single bond	H	CH_3	H

Ex: #	R^1	R^2	R_5	A	B	E	P
405	Cl	X	CN_4H	single bond	H	C_2H_5	H
406	Cl	X	CN_4H	$-CH_2CH_2-$ 	*	H	$COCH_3$
407	Cl	X	CO_2H	single bond	H	H	$COCH_2Cl$
408	Cl	X	CO_2H	single bond	H	H	COC_4H_9
409	Cl	X	CO_2H	single bond	H	CH_3	$COCH_3$
410	Cl	X	CO_2H	single bond	H	C_2H_5	$COCH_3$
411	Cl	X	CN_4H	$-CH_2-CH_2-$ 	*	H	H
412	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
413	Cl	X	CN_4H	single bond	H	H	COC_4H_9
414	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$
415	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$

Ex: #	R^1	R^2	R_5	A	B	E	P
416	Cl	X	CN_4H		*	H	$COCH_3$
417	Cl	X	CO_2H	single bond	H	CH_3	H
418	Cl	X	CO_2H	single bond	H	C_2H_5	H
419	Cl	X	CN_4H		*	H	H
420	Cl	X	CN_4H	single bond	H	CH_3	H
421	Cl	X	CN_4H	single bond	H	C_2H_5	H
422	Cl	X	CN_4H		*	H	$COCH_3$
423	Cl	X	CN_4H	single bond	H	H	$COCH_2Cl$
424	Cl	X	CN_4H	single bond	H	H	COC_4H_9
425	Cl	X	CN_4H	single bond	H	CH_3	$COCH_3$

Ex: #	R^1	R^2	R_5	A	B	E	P
426	Cl	X	CN_4H	single bond	H	C_2H_5	$COCH_3$
427	Cl	X	CN_4H		*	H	H
428	Cl	X	CN_4H	single bond	H	CH_3	H
429	Cl	X	CN_4H	single bond	H	C_2H_5	H
430	X	Cl	CO_2H	single bond	H	H	$COCH_3$
431	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
432	X	Cl	CO_2H	single bond	H	H	COC_4H_9
433	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
434	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
435	X	Cl	CN_4H	single bond	H	H	$COCH_3$
436	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$

Ex: #	R^1	R^2	R_5	A	B	E	P
437	X	Cl	CN_4H	single bond	H	H	COC_4H_9
438	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
439	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
440	X	Cl	CO_2H	single bond	H	H	H
441	X	Cl	CO_2H	single bond	H	CH_3	H
442	X	Cl	CO_2H	single bond	H	C_2H_5	H
443	X	Cl	CN_4H	single bond	H	H	H
444	X	Cl	CN_4H	single bond	H	CH_3	H
445	X	Cl	CN_4H	single bond	H	C_2H_5	H
446	X	Cl	CO_2H	$-CH_2-$	H	H	$COCH_3$
447	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$

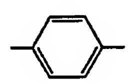
Ex: #	R^1	R^2	R_5	A	B	E	P
448	X	Cl	CO_2H	single bond	H	H	COC_4H_9
449	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
450	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
451	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
452	X	Cl	CN_4H	single bond	H	H	COC_4H_9
453	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
454	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
455	X	Cl	CO_2H	$-CH_2-$	H	H	H
456	X	Cl	CO_2H	single bond	H	CH_3	H
457	X	Cl	CO_2H	single bond	H	C_2H_5	H
458	X	Cl	CN_4H	$-CH_2-$	H	H	H

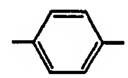
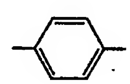
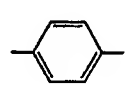
Ex: #	R^1	R^2	R_5	A	B	E	P
459	X	Cl	CN_4H	single bond	H	CH_3	H
460	X	Cl	CN_4H	single bond	H	C_2H_5	H
461	X	Cl	CN_4H	$-CH_2-$	CH_3	H	H
462	X	Cl	CN_4H	$-CH_2-$	CH_3	H	$COCH_3$
463	X	Cl	CO_2H	$-CH_2CH_2-$	H	H	$COCH_3$
464	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
465	X	Cl	CO_2H	single bond	H	H	COC_4H_9
466	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
467	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
468	X	Cl	CN_4H	$-CH_2CH_2-$	H	H	$COCH_3$
469	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
470	X	Cl	CN_4H	single bond	H	H	COC_4H_9

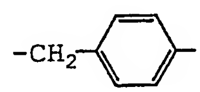
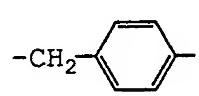
Ex: #	R^1	R^2	R_5	A	B	E	P
471	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
472	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
473	X	Cl	CO_2H	$-CH_2CH_2-$	H	H	H
474	X	Cl	CO_2H	single bond	H	CH_3	H
475	X	Cl	CO_2H	single bond	H	C_2H_5	H
476	X	Cl	CN_4H	$-CH_2CH_2-$	H	H	H
477	X	Cl	CN_4H	single bond	H	CH_3	H
478	X	Cl	CN_4H	single bond	H	C_2H_5	H
479	X	Cl	CO_2H	C_3H_6 (n)	H	H	$COCH_3$
480	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
481	X	Cl	CO_2H	single bond	H	H	COC_4H_9

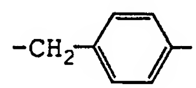
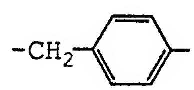
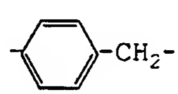
Ex: #	R^1	R^2	R_5	A	B	E	P
482	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
483	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
484	X	Cl	CN_4H	C_3H_6 (n)	H	H	$COCH_3$
485	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
486	X	Cl	CN_4H	single bond	H	H	COC_4H_9
487	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
488	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
489	X	Cl	CO_2H	C_3H_6 (n)	H	H	H
490	X	Cl	CO_2H	single bond	H	CH_3	H
491	X	Cl	CO_2H	single bond	H	C_2H_5	H
492	X	Cl	CN_4H	C_3H_6 (n)	H	H	H

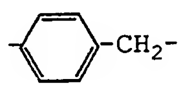
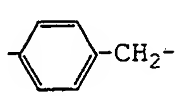
Ex: #	R^1	R^2	R_5	A	B	E	P
493	X	Cl	CN_4H	single bond	H	CH_3	H
494	X	Cl	CN_4H	single bond	H	C_2H_5	H
495	X	Cl	CO_2H	C_4H_8 (n)	H	H	$COCH_3$
496	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
497	X	Cl	CO_2H	single bond	H	H	COC_4H_9
498	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
499	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
500	X	Cl	CN_4H	C_4H_8 (n)	H	H	$COCH_3$
501	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
502	X	Cl	CN_4H	single bond	H	H	COC_4H_9
503	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$

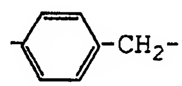
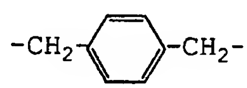
Ex: #	R^1	R^2	R_5	A	B	E	P
504	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
505	X	Cl	CO_2H	C_4H_8 (n)	H	H	H
506	X	Cl	CO_2H	single bond	H	CH_3	H
507	X	Cl	CO_2H	single bond	H	C_2H_5	H
508	X	Cl	CN_4H	C_4H_8 (n)	H	H	H
509	X	Cl	CN_4H	single bond	H	CH_3	H
510	X	Cl	CN_4H	single bond	H	C_2H_5	H
511	X	Cl	CO_2H		H	H	$COCH_3$
512	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
513	X	Cl	CO_2H	single bond	H	H	COC_4H_9
514	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$

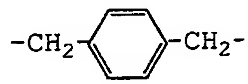
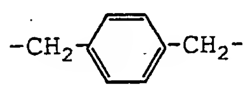
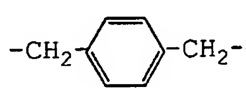
Ex: #	R^1	R^2	R_5	A	B	E	P
515	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
516	X	Cl	CN_4H		H	H	$COCH_3$
517	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
518	X	Cl	CN_4H	single bond	H	H	COC_4H_9
519	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
520	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
521	X	Cl	CO_2H		H	H	H
522	X	Cl	CO_2H	single bond	H	CH_3	H
523	X	Cl	CO_2H	single bond	H	C_2H_5	H
524	X	Cl	CN_4H		H	H	H

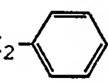
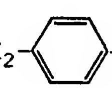
Ex: #	R^1	R^2	R_5	A	B	E	P
525	X	Cl	CN_4H	single bond	H	CH_3	H
526	X	Cl	CN_4H	single bond	H	C_2H_5	H
527	X	Cl	CO_2H		H	H	$COCH_3$
528	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
529	X	Cl	CO_2H	single bond	H	H	COC_4H_9
530	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
531	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
532	X	Cl	CN_4H		H	H	$COCH_3$
533	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
534	X	Cl	CN_4H	single bond	H	H	COC_4H_9

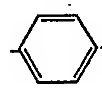
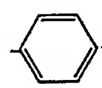
Ex: #	R^1	R^2	R_5	A	B	E	P
535	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
536	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
537	X	Cl	CO_2H		H	H	H
538	X	Cl	CO_2H	single bond	H	CH_3	H
539	X	Cl	CO_2H	single bond	H	C_2H_5	H
540	X	Cl	CN_4H		H	H	H
541	X	Cl	CN_4H	single bond	H	CH_3	H
542	X	Cl	CN_4H	single bond	H	C_2H_5	H
543	X	Cl	CO_2H		H	H	$COCH_3$
544	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$

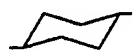
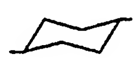
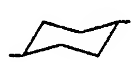
Ex: #	R^1	R^2	R_5	A	B	E	P
545	X	Cl	CO_2H	single bond	H	H	COC_4H_9
546	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
547	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
548	X	Cl	CN_4H		H	H	$COCH_3$
549	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
550	X	Cl	CN_4H	single bond	H	H	COC_4H_9
551	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
552	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
553	X	Cl	CO_2H		H	H	H
554	X	Cl	CO_2H	single bond	H	CH_3	H

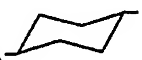
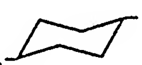
Ex: #	R^1	R^2	R_5	A	B	E	P
555	X	Cl	CO_2H	single bond	H	C_2H_5	H
556	X	Cl	CN_4H		H	H	H
557	X	Cl	CN_4H	single bond	H	CH_3	H
558	X	Cl	CN_4H	single bond	H	C_2H_5	H
559	X	Cl	CO_2H		H	H	$COCH_3$
560	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
561	X	Cl	CO_2H	single bond	H	H	COC_4H_9
562	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
563	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$

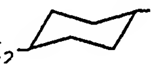
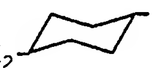
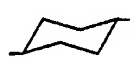
Ex: #	R^1	R^2	R_5	A	B	E	P
564	X	Cl	CN_4H		H	H	$COCH_3$
565	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
566	X	Cl	CN_4H	single bond	H	H	COC_4H_9
567	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
568	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
569	X	Cl	CO_2H		H	H	H
570	X	Cl	CO_2H	single bond	H	CH_3	H
571	X	Cl	CO_2H	single bond	H	C_2H_5	H
572	X	Cl	CN_4H		H	H	H
573	X	Cl	CN_4H	single bond	H	CH_3	H

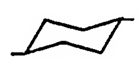
Ex: #	R^1	R^2	R_5	A	B	E	P
574	X	Cl	CN_4H	single bond	H	C_2H_5	H
575	X	Cl	CN_4H	$-CH_2CH_2-$-	H	H	$COCH_3$
576	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
577	X	Cl	CO_2H	single bond	H	H	COC_4H_9
578	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
579	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
580	X	Cl	CN_4H	$-CH_2CH_2-$-	H	H	H
581	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
582	X	Cl	CN_4H	single bond	H	H	COC_4H_9
583	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$

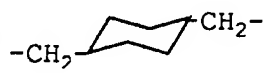
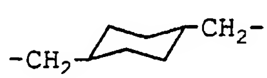
Ex: #	R^1	R^2	R_5	A	B	E	P
584	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
585	X	Cl	CN_4H	$-CH_2-CH_2-$	H	H	$COCH_3$
586	X	Cl	CO_2H	single bond	H	CH_3	H
587	X	Cl	CO_2H	single bond	H	C_2H_5	H
588	X	Cl	CN_4H	$-CH_2-CH_2-$	H	H	H
589	X	Cl	CN_4H	single bond	H	CH_3	H
590	X	Cl	CN_4H	single bond	H	C_2H_5	H
591	X	Cl	CO_2H		H	H	$COCH_3$
592	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
593	X	Cl	CO_2H	single bond	H	H	COC_4H_9

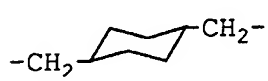
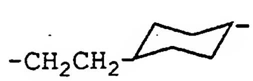
Ex: #	R^1	R^2	R_5	A	B	E	P
594	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
595	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
596	X	Cl	CN_4H		H	H	$COCH_3$
597	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
598	X	Cl	CN_4H	single bond	H	H	COC_4H_9
599	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
600	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
601	X	Cl	CO_2H		H	H	H
602	X	Cl	CO_2H	single bond	H	CH_3	H
603	X	Cl	CO_2H	single bond	H	C_2H_5	H
604	X	Cl	CN_4H		H	H	H

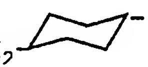
Ex: #	R^1	R^2	R_5	A	B	E	P
605	X	Cl	CN_4H	single bond	H	CH_3	H
606	X	Cl	CN_4H	single bond	H	C_2H_5	H
607	X	Cl	CO_2H	$-CH_2-$ 	H	H	$COCH_3$
608	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
609	X	Cl	CO_2H	single bond	H	H	COC_4H_9
610	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
611	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
612	X	Cl	CN_4H	$-CH_2-$ 	H	H	$COCH_3$
613	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
614	X	Cl	CN_4H	single bond	H	H	COC_4H_9
615	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$

Ex: #	R^1	R^2	R_5	A	B	E	P
616	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
617	X	Cl	CO_2H	$-CH_2-$ 	H	H	H
618	X	Cl	CO_2H	single bond	H	CH_3	H
619	X	Cl	CO_2H	single bond	H	C_2H_5	H
620	X	Cl	CN_4H	$-CH_2-$ 	H	H	H
621	X	Cl	CN_4H	single bond	H	CH_3	H
622	X	Cl	CN_4H	single bond	H	C_2H_5	H
623	X	Cl	CO_2H	 CH_2-	H	H	$COCH_3$
624	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
625	X	Cl	CO_2H	single bond	H	H	COC_4H_9

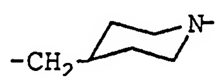
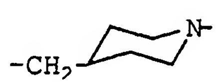
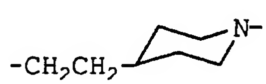
Ex: #	R^1	R^2	R_5	A	B	E	P
626	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
627	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
628	X	Cl	CN_4H	 $-CH_2-$	H	H	$COCH_3$
629	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
630	X	Cl	CN_4H	single bond	H	H	COC_4H_9
631	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
632	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
633	X	Cl	CO_2H	 $-CH_2-$	H	H	H
634	X	Cl	CO_2H	single bond	H	CH_3	H
635	X	Cl	CO_2H	single bond	H	C_2H_5	H

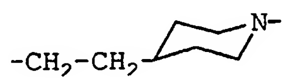
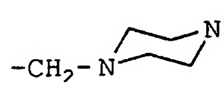
Ex: #	R^1	R^2	R_5	A	B	E	P
636	X	Cl	CN_4H		H	H	H
637	X	Cl	CN_4H	single bond	H	CH_3	H
638	X	Cl	CN_4H	single bond	H	C_2H_5	H
639	X	Cl	CO_2H		H	H	$COCH_3$
640	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
641	X	Cl	CO_2H	single bond	H	H	COC_4H_9
642	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
643	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
644	X	Cl	CN_4H		H	H	$COCH_3$
645	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$

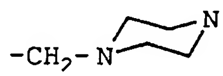
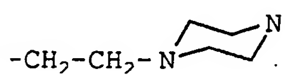
Ex: #	R^1	R^2	R_5	A	B	E	P
646	X	Cl	CN_4H	single bond	H	H	COC_4H_9
647	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
648	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
649	X	Cl	CO_2H		H	H	H
650	X	Cl	CO_2H	single bond	H	CH_3	H
651	X	Cl	CO_2H	single bond	H	C_2H_5	H
652	X	Cl	CN_4H		H	H	H
653	X	Cl	CN_4H	single bond	H	CH_3	H
654	X	Cl	CN_4H	single bond	H	C_2H_5	H
655	X	Cl	CN_4H		H	H	$COCH_3$
656	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$

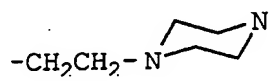
Ex: #	R^1	R^2	R_5	A	B	E	P
657	X	Cl	CO_2H	single bond	H	H	COC_4H_9
658	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
659	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
660	X	Cl	CN_4H	$-CH_2CH_2-$ 	H	H	H
661	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
662	X	Cl	CN_4H	single bond	H	H	COC_4H_9
663	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
664	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
665	X	Cl	CN_4H	 CH_2CH_2-	H	H	$COCH_3$
666	X	Cl	CO_2H	single bond	H	CH_3	H

Ex: #	R^1	R^2	R_5	A	B	E	P
667	X	Cl	CO_2H	single bond	H	C_2H_5	H
668	X	Cl	CN_4H		H	H	H
669	X	Cl	CN_4H	single bond	H	CH_3	H
670	X	Cl	CN_4H	single bond	H	C_2H_5	H
671	X	Cl	CN_4H		*	H	$COCH_3$
672	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
673	X	Cl	CO_2H	single bond	H	H	COC_4H_9
674	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
675	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
676	X	Cl	CN_4H		*	H	H
677	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$

Ex: #	R^1	R^2	R_5	A	B	E	P
678	X	Cl	CN_4H	single bond	H	H	COC_4H_9
679	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
680	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
681	X	Cl	CN_4H		*	H	$COCH_3$
682	X	Cl	CO_2H	single bond	H	CH_3	H
683	X	Cl	CO_2H	single bond	H	C_2H_5	H
684	X	Cl	CN_4H		*	H	H
685	X	Cl	CN_4H	single bond	H	CH_3	H
686	X	Cl	CN_4H	single bond	H	C_2H_5	H
687	X	Cl	CN_4H		*	H	$COCH_3$

Ex: #	R^1	R^2	R_5	A	B	E	P
688	X	Cl	CO_2H	single bond	H	H	$COCH_2Cl$
689	X	Cl	CO_2H	single bond	H	H	COC_4H_9
690	X	Cl	CO_2H	single bond	H	CH_3	$COCH_3$
691	X	Cl	CO_2H	single bond	H	C_2H_5	$COCH_3$
692	X	Cl	CN_4H		*	H	H
693	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
694	X	Cl	CN_4H	single bond	H	H	COC_4H_9
695	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
696	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$
697	X	Cl	CN_4H		*	H	$COCH_3$

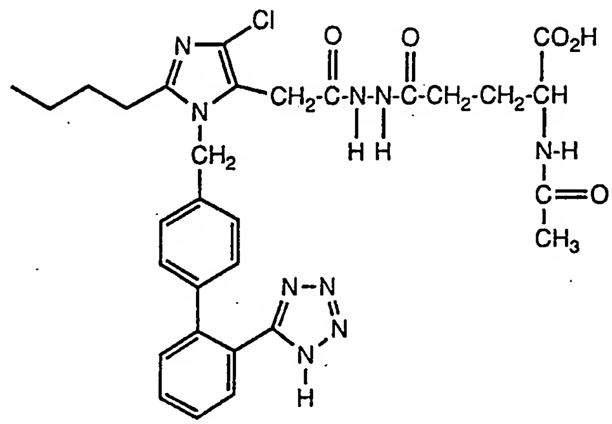
Ex: #	R^1	R^2	R_5	A	B	E	P
698	X	Cl	CO_2H	single bond	H	CH_3	H
699	X	Cl	CO_2H	single bond	H	C_2H_5	H
700	X	Cl	CN_4H		*	H	H
701	X	Cl	CN_4H	single bond	H	CH_3	H
702	X	Cl	CN_4H	single bond	H	C_2H_5	H
703	X	Cl	CN_4H		*	H	$COCH_3$
704	X	Cl	CN_4H	single bond	H	H	$COCH_2Cl$
705	X	Cl	CN_4H	single bond	H	H	COC_4H_9
706	X	Cl	CN_4H	single bond	H	CH_3	$COCH_3$
707	X	Cl	CN_4H	single bond	H	C_2H_5	$COCH_3$

Ex: #	R^1	R^2	R_5	A	B	E	P
708	X	Cl	CN_4H		*	H	H
709	X	Cl	CN_4H	single bond	H	CH_3	H
710	X	Cl	CN_4H	single bond	H	C_2H_5	H

*B is incorporated in A

Another class of highly preferred specific conjugates of the invention is provided by conjugates formed from a biphenylmethyl 1H-substituted imidazole AII antagonist compound having a terminal carboxyl group attached to the imidazo nucleus. In this family of conjugates, the cleavable glutamyl residue is attached through a diamino linker moiety which connects the imidazo AII antagonist terminal carboxylic moiety through two amide bonds to the gamma carbon of the glutamyl residue Such conjugates are shown as Examples 711-1526. General procedures for preparation of the conjugates of Examples #711-#1526 are described in Schemes VI-VII. Detailed procedures for preparation of representative conjugates are described in Examples #711 and #712. Procedures similar to these aforementioned general and specific procedures may be used for preparation of the conjugates identified as Examples #711-#1526 shown in Table VII.

Example 711



N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide

Step 1: Preparation of 2-butyl-5-cyanomethyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

Thionyl chloride (7.2 mL, 98 mmol) is slowly dripped into a solution of 8.45 g (20.0 mmol) of the compound of Example 78 in a minimum of chloroform. The mixture is stirred for 2 h at ambient temperature and the solvent is removed in vacuo. The chloride is dissolved in dimethylsulfoxide (DMSO) and is added to a solution of 5.80 g (118 mmol) of sodium cyanide in 400 mL of DMSO. The solution is stirred overnight under nitrogen at ambient temperature; water is added and the aqueous layer is extracted with ethyl acetate. The extracts are combined, are dried ($MgSO_4$), and are concentrated in vacuo to give the crude product. Purification by silica gel chromatography (Waters DeltaPrep-500A) provides the pure 5-cyanomethyl derivative.

Step 2: Preparation of 2-butyl-5-carboxymethyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

A solution of 6.5 g (15 mmol) of the 5-cyanomethyl derivative from step 1 in 150 mL of concentrated hydrochloric acid/acetic acid (1:1) is stirred at reflux overnight. The solvents are removed *in vacuo* to give the crude product. Purification by reverse phase chromatography (Waters Deltaprep-3000) provides the pure 5-acetic acid derivative.

Step 3: Preparation of 2-butyl-4-chloro-5-methoxycarbonylmethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

A solution of 4.5 g (10 mmol) of the 5-acetic acid derivative from step 2 in 150 mL of absolute methanol is cooled to -10°C and is treated with 1.5 mL (20 mmol) of thionyl chloride under nitrogen. The reaction is allowed to warm to ambient temperature and is stirred at reflux overnight. The methanol is removed *in vacuo* and the crude product is dissolved in water. The pH is adjusted to pH 4 with 1*N* NaOH and the solution is extracted with ethyl acetate. The extracts are combined, are dried ($MgSO_4$), and are concentrated *in vacuo* to give the crude product. Purification by silica gel chromatography (Waters Prep-500A) provides the pure 5-methyl acetate derivative.

Step 4: Preparation of 2-butyl-4-chloro-5-hydrazinylcarbonyl-methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

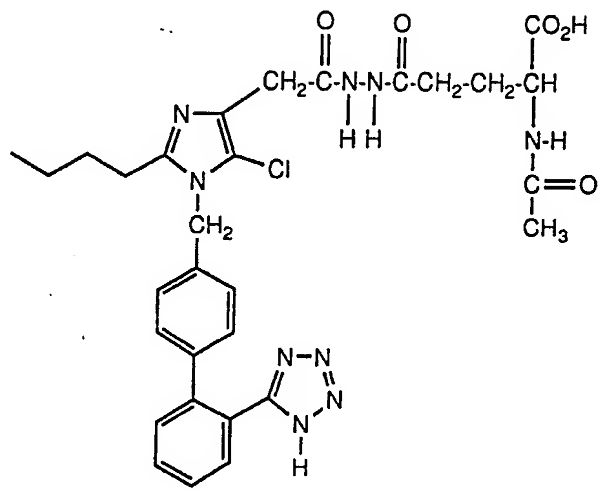
Under nitrogen, 2.32 g (5.0 mmol) of the 5-methyl acetate derivative from step 3 is dissolved in 50 mL of methanol and is treated with 5mL (160 mmol) of anhydrous hydrazine. The reaction is allowed to stir at reflux

overnight; concentration in vacuo gives the crude material. Purification by silica gel chromatography (Waters Prep-500A) provides the pure 5-acetic acid hydrazide derivative.

Step 5: Preparation of N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide

To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid-α-tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicylcohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of the hydrazide from step 4 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K_2CO_3. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K_2CO_3 is added every 30 min for 5 h; the pH is mainained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) gives the pure product.

Example 712



N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide

Step 1: Preparation of 2-butyl-4-cyanomethyl-5-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

Thionyl chloride (7.2 mL, 98 mmol) is slowly dripped into a solution of 8.45 g (20.0 mmol) of the compound of Example 79 in a minimum of chloroform. The mixture is stirred for 2 h at ambient temperature and the solvent is removed in vacuo. The chloride is dissolved in DMSO and is added to a solution of 5.80 g (118 mmol) of sodium cyanide in 400 mL of DMSO. The solution is stirred overnight under nitrogen at ambient temperature; water is added and the aqueous layer is extracted with ethyl acetate. The extracts are combined, are dried ($MgSO_4$), and are concentrated in vacuo to give the crude product. Purification by silica gel chromatography (Waters Prep-500A) provides the pure 4-cyanomethyl derivative.

Step 2: Preparation of 2-butyl-4-carboxymethyl-5-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

A solution of 6.5 g (15 mmol) of the 4-cyanomethyl derivative from step 1 in 150 mL of concentrated hydrochloric acid/acetic acid (1:1) is stirred at reflux overnight. The solvents are removed in vacuo to give the crude product. Purification by reverse phase chromatography provides (Waters Deltaprep-3000) the pure 4-acetic acid derivative.

Step 3: Preparation of 2-butyl-5-chloro-4-methoxycarbonylmethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

A solution of 4.5 g (10 mmol) of the 4-acetic acid derivative from step 2 in 150 mL of absolute methanol is cooled to -10°C and is treated with 1.5 mL (20 mmol) of thionyl chloride under nitrogen. The reaction is allowd to warm to ambient temperature and is stirred at reflux overnight. The methanol is removed in vacuo and the crude product is dissolved in water. The pH is adjusted to pH 4 with 1N NaOH and the solution is extracted with ethyl acetate. The extracts are combined, are dried ($MgSO_4$), and are concentrated in vacuo to give the crude product. Purification by silica gel chromatography (Waters Prep-500A) provides the pure 4-methyl acetate derivative.

Step 4: Preparation of 2-butyl-5-chloro-4-hydrazinylcarbonylmethyl-1-[(2'-(1H-tetrazole-5-yl)biphenyl-4-methyl]imidazole.

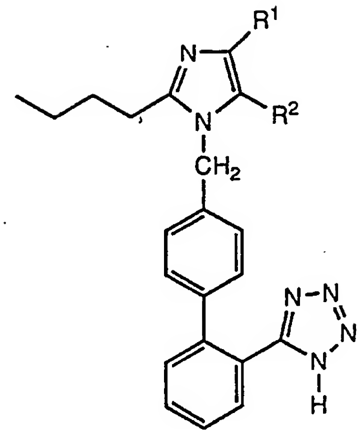
Under nitrogen, 2.32 g (5.0 mmol) of the 4-methyl acetate derivative from step 3 is dissolved in 50 mL of methanol and is treated with 5 mL (160 mmol) of anhydrous hydrazine. The reaction is allowed to stir at reflux

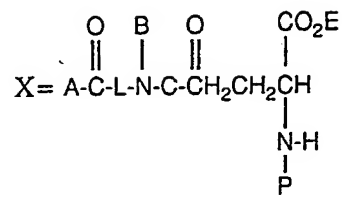
overnihgt; concentration *in vacuo* gives the crude material. Purification by silica gel chromatography (Waters Prep-500A) provides the pure 4-acetic acid hydrazide derivative.

Step 5: Preparation of N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide

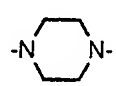
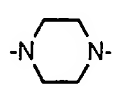
To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid-α-tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicylcohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of the hydrazide from step 4 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated *in vacuo*. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K_2CO_3. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K_2CO_3 is added every 30 min for 5 h; the pH is mainained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) gives the pure product.

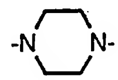
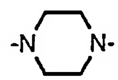
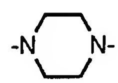
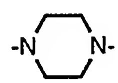
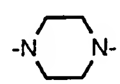
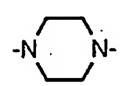
TABLE VII



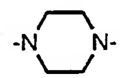
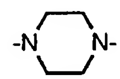
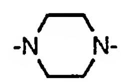
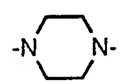
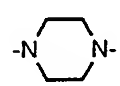
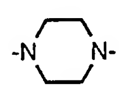


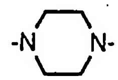
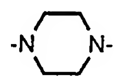
Ex. #	R^1	R^2	A	L	B	E	P
713	Cl	X	single bond	-NH-	H	H	$COCH_3$
714	Cl	X	single bond	-NH-	H	H	$COCH_2Cl$
715	Cl	X	single bond	-NH-	H	H	COC_4H_9
716	Cl	X	single bond	-NH-	H	CH_3	$COCH_3$
717	Cl	X	single bond	-NH-	H	C_2H_5	$COCH_3$
718	Cl	X	single bond	-NH-	H	H	H
719	Cl	X	single bond	-NH-	H	CH_3	H
720	Cl	X	single bond	-NH-	H	C_2H_5	H

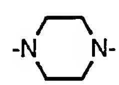
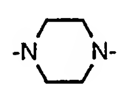
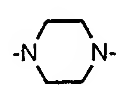
Ex. #	R^1	R^2	A	L	B	E	P
721	Cl	X	single bond	$-NHCH_2CH_2-$	H	H	$COCH_3$
722	Cl	X	single bond	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
723	Cl	X	single bond	$-NHCH_2CH_2-$	H	H	COC_4H_9
724	Cl	X	single bond	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
725	Cl	X	single bond	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
726	Cl	X	single bond	$-NHCH_2CH_2-$	H	H	H
727	Cl	X	single bond	$-NHCH_2CH_2-$	H	CH_3	H
728	Cl	X	single bond	$-NHCH_2CH_2-$	H	C_2H_5	H
729	Cl	X	single bond		*	H	$COCH_3$
730	Cl	X	single bond		H	H	$COCH_2Cl$

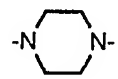
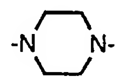
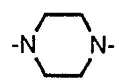
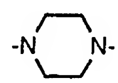
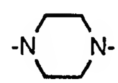
Ex. #	R^1	R^2	A	L	B	E	P
731	Cl	X	single bond		H	H	COC_4H_9
732	Cl	X	single bond		H	CH_3	$COCH_3$
733	Cl	X	single bond		H	C_2H_5	$COCH_3$
734	Cl	X	single bond		*	H	H
735	Cl	X	single bond		H	CH_3	H
736	Cl	X	single bond		H	C_2H_5	H
737	Cl	X	CH_2	-NH-	H	H	$COCH_2Cl$
738	Cl	X	CH_2	-NH-	H	H	COC_4H_9

Ex. #	R^1	R^2	A	L	B	E	P
739	Cl	X	CH_2	-NH-	H	CH_3	$COCH_3$
740	Cl	X	CH_2	-NH-	H	C_2H_5	$COCH_3$
741	Cl	X	CH_2	-NH-	H	H	H
742	Cl	X	CH_2	-NH-	H	CH_3	H
743	Cl	X	CH_2	-NH-	H	C_2H_5	H
744	Cl	X	CH_2	$-NHCH_2CH_2-$	H	H	$COCH_3$
745	Cl	X	CH_2	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
746	Cl	X	CH_2	$-NHCH_2CH_2-$	H	H	COC_4H_9
747	Cl	X	CH_2	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
748	Cl	X	CH_2	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
749	Cl	X	CH_2	$-NHCH_2CH_2-$	H	H	H

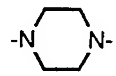
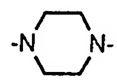
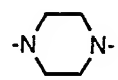
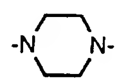
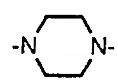
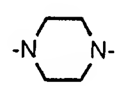
Ex. #	R^1	R^2	A	L	B	E	P
750	Cl	X	CH_2	$-NHCH_2CH_2-$	H	CH_3	H
751	Cl	X	CH_2	$-NHCH_2CH_2-$	H	C_2H_5	H
752	Cl	X	CH_2		*	H	$COCH_3$
753	Cl	X	CH_2		H	H	$COCH_2Cl$
754	Cl	X	CH_2		H	H	COC_4H_9
755	Cl	X	CH_2		H	CH_3	$COCH_3$
756	Cl	X	CH_2		H	C_2H_5	$COCH_3$
757	Cl	X	CH_2		*	H	H

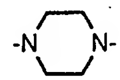
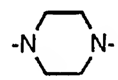
Ex. #	R^1	R^2	A	L	B	E	P
758	Cl	X	CH_2		H	CH_3	H
759	Cl	X	CH_2		H	C_2H_5	H
760	Cl	X	CH_2CH_2	-NH-	H	H	$COCH_3$
761	Cl	X	CH_2CH_2	-NH-	H	H	$COCH_2Cl$
762	Cl	X	CH_2CH_2	-NH-	H	H	COC_4H_9
763	Cl	X	CH_2CH_2	-NH-	H	CH_3	$COCH_3$
764	Cl	X	CH_2CH_2	-NH-	H	C_2H_5	$COCH_3$
765	Cl	X	CH_2CH_2	-NH-	H	H	H
766	Cl	X	CH_2CH_2	-NH-	H	CH_3	H
767	Cl	X	CH_2CH_2	-NH-	H	C_2H_5	H
768	Cl	X	CH_2CH_2	$-NHCH_2CH_2-$	H	H	$COCH_3$

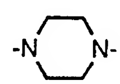
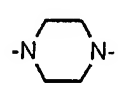
Ex. #	R^1	R^2	A	L	B	E	P
769	Cl	X	CH_2CH_2	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
770	Cl	X	CH_2CH_2	$-NHCH_2CH_2-$	H	H	COC_4H_9
771	Cl	X	CH_2CH_2	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
772	Cl	X	CH_2CH_2	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
773	Cl	X	CH_2CH_2	$-NHCH_2CH_2-$	H	H	H
774	Cl	X	CH_2CH_2	$-NHCH_2CH_2-$	H	CH_3	H
775	Cl	X	CH_2CH_2	$-NHCH_2CH_2-$	H	C_2H_5	H
776	Cl	X	CH_2CH_2		*	H	$COCH_3$
777	Cl	X	CH_2CH_2		H	H	$COCH_2Cl$
778	Cl	X	CH_2CH_2		H	H	COC_4H_9

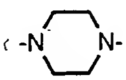
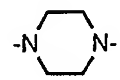
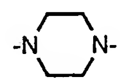
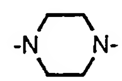
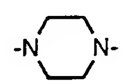
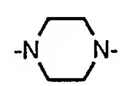
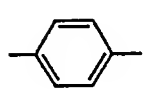
Ex. #	R^1	R^2	A	L	B	E	P
779	Cl	X	CH_2CH_2		H	CH_3	$COCH_3$
780	Cl	X	CH_2CH_2		H	C_2H_5	$COCH_3$
781	Cl	X	CH_2CH_2		*	H	H
782	Cl	X	CH_2CH_2		H	CH_3	H
783	Cl	X	CH_2CH_2		H	C_2H_5	H
784	Cl	X	C_3H_6 (n)	-NH-	H	H	$COCH_3$
785	Cl	X	C_3H_6 (n)	-NH-	H	H	$COCH_2Cl$
786	Cl	X	C_3H_6 (n)	-NH-	H	H	COC_4H_9

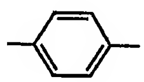
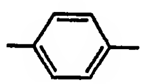
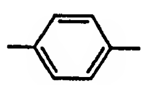
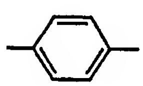
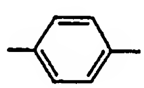
Ex. #	R^1	R^2	A	L	B	E	P
787	Cl	X	C_3H_6 (n)	-NH-	H	CH_3	$COCH_3$
788	Cl	X	C_3H_6 (n)	-NH-	H	C_2H_5	$COCH_3$
789	Cl	X	C_3H_6 (n)	-NH-	H	H	H
790	Cl	X	C_3H_6 (n)	-NH-	H	CH_3	H
791	Cl	X	C_3H_6 (n)	-NH-	H	C_2H_5	H
792	Cl	X	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	$COCH_3$
793	Cl	X	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
794	Cl	X	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	COC_4H_9
795	Cl	X	C_3H_6 (n)	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
796	Cl	X	C_3H_6 (n)	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
797	Cl	X	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	H

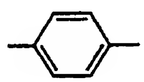
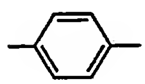
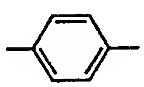
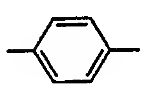
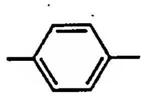
Ex. #	R^1	R^2	A	L	B	E	P
798	Cl	X	C_3H_6 (n)	$-NHCH_2CH_2-$	H	CH_3	H
799	Cl	X	C_3H_6 (n)	$-NHCH_2CH_2-$	H	C_2H_5	H
800	Cl	X	C_3H_6 (n)		*	H	$COCH_3$
801	Cl	X	C_3H_6 (n)		H	H	$COCH_2Cl$
802	Cl	X	C_3H_6 (n)		H	H	COC_4H_9
803	Cl	X	C_3H_6 (n)		H	CH_3	$COCH_3$
804	Cl	X	C_3H_6 (n)		H	C_2H_5	$COCH_3$
805	Cl	X	C_3H_6 (n)		*	H	H

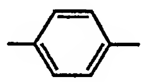
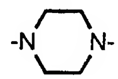
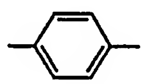
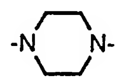
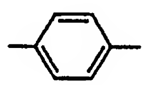
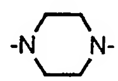
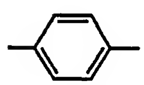
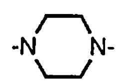
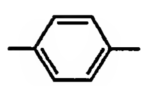
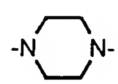
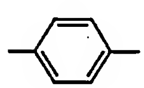
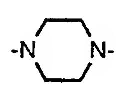
Ex. #	R^1	R^2	A	L	B	E	P
806	Cl	X	C_3H_6 (n)		H	CH_3	H
807	Cl	X	C_3H_6 (n)		H	C_2H_5	H
808	Cl	X	C_4H_8 (n)	-NH-	H	H	$COCH_3$
809	Cl	X	C_4H_8 (n)	-NH-	H	H	$COCH_2Cl$
810	Cl	X	C_4H_8 (n)	-NH-	H	H	COC_4H_9
811	Cl	X	C_4H_8 (n)	-NH-	H	CH_3	$COCH_3$
812	Cl	X	C_4H_8 (n)	-NH-	H	C_2H_5	$COCH_3$
813	Cl	X	C_4H_8 (n)	-NH-	H	H	H
814	Cl	X	C_4H_8 (n)	-NH-	H	CH_3	H
815	Cl	X	C_4H_8 (n)	-NH-	H	C_2H_5	H
816	Cl	X	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	$COCH_3$

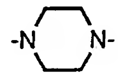
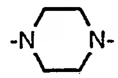
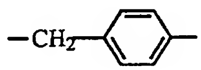
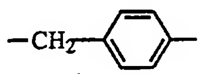
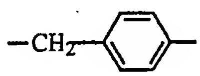
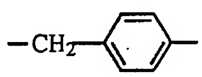
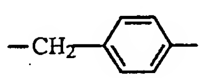
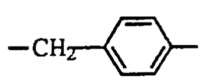
Ex. #	R^1	R^2	A	L	B	E	P
817	Cl	X	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
818	Cl	X	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	COC_4H_9
819	Cl	X	C_4H_8 (n)	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
820	Cl	X	C_4H_8 (n)	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
821	Cl	X	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	H
822	Cl	X	C_4H_8 (n)	$-NHCH_2CH_2-$	H	CH_3	H
823	Cl	X	C_4H_8 (n)	$-NHCH_2CH_2-$	H	C_2H_5	H
824	Cl	X	C_4H_8 (n)		*	H	$COCH_3$
825	Cl	X	C_4H_8 (n)		H	H	$COCH_2Cl$

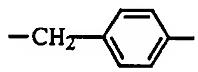
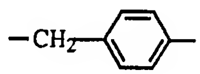
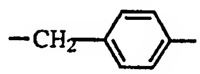
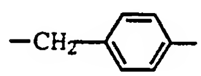
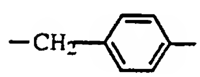
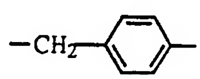
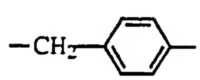
Ex. #	R^1	R^2	A	L	B	E	P
826	Cl	X	C_4H_8 (n)		H	H	COC_4H_9
827	Cl	X	C_4H_8 (n)		H	CH_3	$COCH_3$
828	Cl	X	C_4H_8 (n)		H	C_2H_5	$COCH_3$
829	Cl	X	C_4H_8 (n)		*	H	H
830	Cl	X	C_4H_8 (n)		H	CH_3	H
831	Cl	X	C_4H_8 (n)		H	C_2H_5	H
832	Cl	X		-NH-	H	H	$COCH_3$

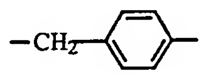
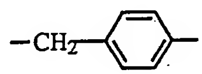
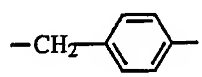
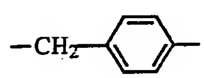
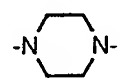
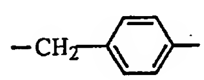
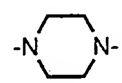
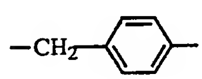
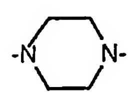
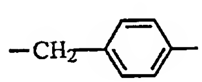
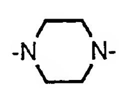
Ex. #	R^1	R^2	A	L	B	E	P
833	Cl	X		-NH-	H	H	$COCH_2Cl$
834	Cl	X		-NH-	H	H	COC_4H_9
835	Cl	X		-NH-	H	CH_3	$COCH_3$
836	Cl	X		-NH-	H	C_2H_5	$COCH_3$
837	Cl	X		-NH-	H	H	H
838	Cl	X		-NH-	H	CH_3	H
839	Cl	X		-NH-	H	C_2H_5	H

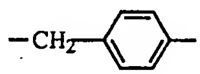
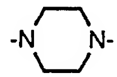
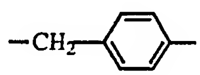
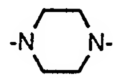
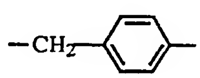
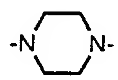
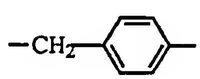
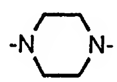
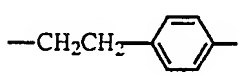
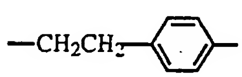
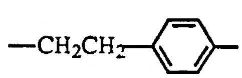
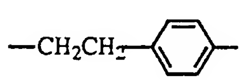
Ex. #	R^1	R^2	A	L	B	E	P
840	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_3$
841	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
842	Cl	X		$-NHCH_2CH_2-$	H	H	COC_4H_9
843	Cl	X		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
844	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
845	Cl	X		$-NHCH_2CH_2-$	H	H	H
846	Cl	X		$-NHCH_2CH_2-$	H	CH_3	H

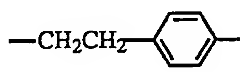
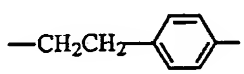
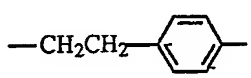
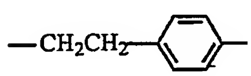
Ex. #	R^1	R^2	A	L	B	E	P
847	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	H
848	Cl	X			*	H	$COCH_3$
849	Cl	X			H	H	$COCH_2Cl$
850	Cl	X			H	H	COC_4H_9
851	Cl	X			H	CH_3	$COCH_3$
852	Cl	X			H	C_2H_5	$COCH_3$
853	Cl	X			*	H	H

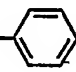
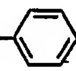
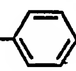
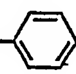
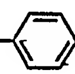
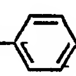
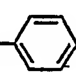
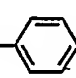
Ex. #	R^1	R^2	A	L	B	E	P
854	Cl	X			H	CH_3	H
855	Cl	X			H	C_2H_5	H
856	Cl	X		-NH-	H	H	$COCH_3$
857	Cl	X		-NH-	H	H	$COCH_2Cl$
858	Cl	X		-NH-	H	H	COC_4H_9
859	Cl	X		-NH-	H	CH_3	$COCH_3$
860	Cl	X		-NH-	H	C_2H_5	$COCH_3$
861	Cl	X		-NH-	H	H	H

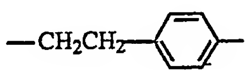
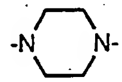
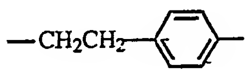
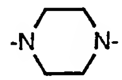
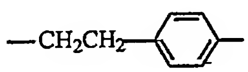
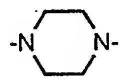
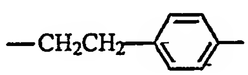
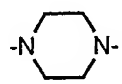
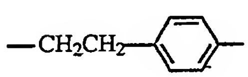
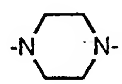
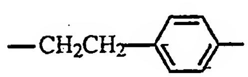
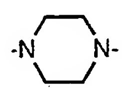
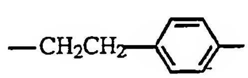
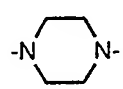
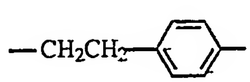
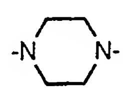
Ex. #	R^1	R^2	A	L	B	E	P
862	Cl	X		-NH-	H	CH_3	H
863	Cl	X		-NH-	H	C_2H_5	H
864	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_3$
865	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
866	Cl	X		$-NHCH_2CH_2-$	H	H	COC_4H_9
867	Cl	X		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
868	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$

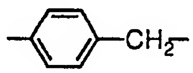
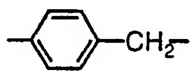
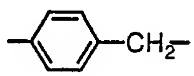
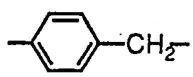
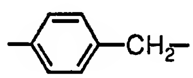
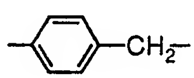
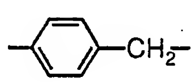
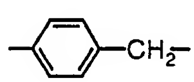
Ex. #	R^1	R^2	A	L	B	E	P
869	Cl	X		$-NHCH_2CH_2-$	H	H	H
870	Cl	X		$-NHCH_2CH_2-$	H	CH_3	H
871	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	H
872	Cl	X			*	H	$COCH_3$
873	Cl	X			H	H	$COCH_2Cl$
874	Cl	X			H	H	COC_4H_9
875	Cl	X			H	CH_3	$COCH_3$

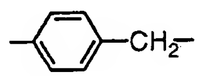
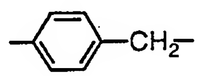
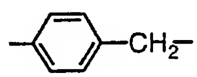
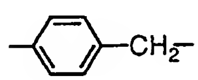
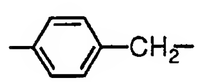
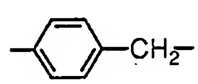
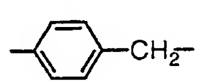
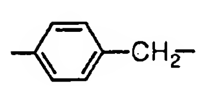
Ex. #	R^1	R^2	A	L	B	E	P
876	Cl	X			H	C_2H_5	$COCH_3$
877	Cl	X			*	H	H
878	Cl	X			H	CH_3	H
879	Cl	X			H	C_2H_5	H
880	Cl	X		-NH-	H	H	$COCH_3$
881	Cl	X		-NH-	H	H	$COCH_2Cl$
882	Cl	X		-NH-	H	H	COC_4H_9
883	Cl	X		-NH-	H	CH_3	$COCH_3$

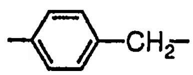
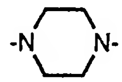
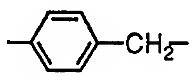
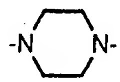
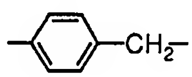
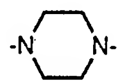
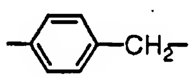
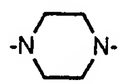
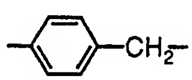
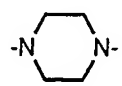
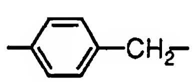
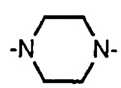
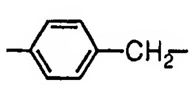
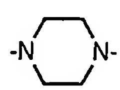
Ex. #	R^1	R^2	A	L	B	E	P
884	Cl	X		-NH-	H	C_2H_5	$COCH_3$
885	Cl	X		-NH-	H	H	H
886	Cl	X		-NH-	H	CH_3	H
887	Cl	X		-NH-	H	C_2H_5	H

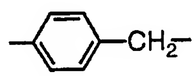
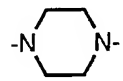
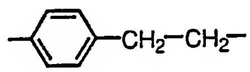
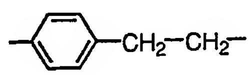
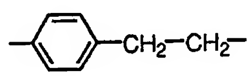
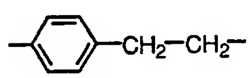
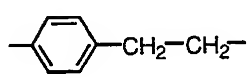
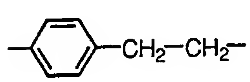
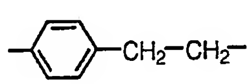
Ex.#	R[1]	R[2]	A	L	B	E	P
888	Cl	X	$—CH_2CH_2—$—	$-NHCH_2CH_2-$	H	H	$COCH_3$
889	Cl	X	$—CH_2CH_2—$—	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
890	Cl	X	$—CH_2CH_2—$—	$-NHCH_2CH_2-$	H	H	COC_4H_9
891	Cl	X	$—CH_2CH_2—$—	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
892	Cl	X	$—CH_2CH_2—$—	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
893	Cl	X	$—CH_2CH_2—$—	$-NHCH_2CH_2-$	H	H	H
894	Cl	X	$—CH_2CH_2—$—	$-NHCH_2CH_2-$	H	CH_3	H
895	Cl	X	$—CH_2CH_2—$—	$-NHCH_2CH_2-$	H	C_2H_5	H

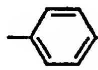
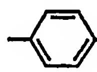
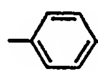
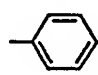
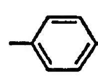
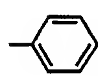
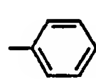
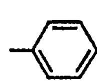
Ex.#	R^1	R^2	A	L	B	E	P
896	Cl	X			*	H	$COCH_3$
897	Cl	X			H	H	$COCH_2Cl$
898	Cl	X			H	H	COC_4H_9
899	Cl	X			H	CH_3	$COCH_3$
900	Cl	X			H	C_2H_5	$COCH_3$
901	Cl	X			*	H	H
902	Cl	X			H	CH_3	H
903	Cl	X			H	C_2H_5	H

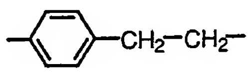
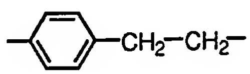
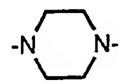
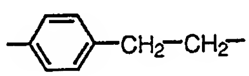
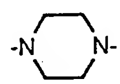
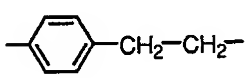
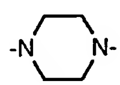
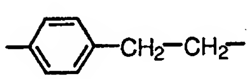
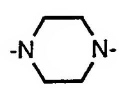
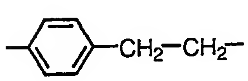
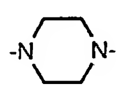
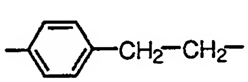
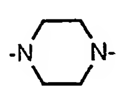
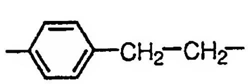
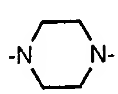
Ex.#	R^1	R^2	A	L	B	E	P
904	Cl	X		-NH-	H	H	$COCH_3$
905	Cl	X		-NH-	H	H	$COCH_2Cl$
906	Cl	X		-NH-	H	H	COC_4H_9
907	Cl	X		-NH-	H	CH_3	$COCH_3$
908	Cl	X		-NH-	H	C_2H_5	$COCH_3$
909	Cl	X		-NH-	H	H	H
910	Cl	X		-NH-	H	CH_3	H
911	Cl	X		-NH-	H	C_2H_5	H

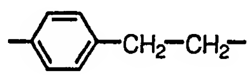
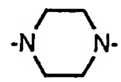
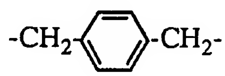
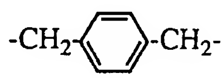
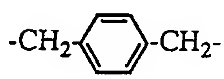
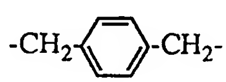
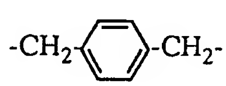
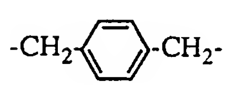
Ex.#	R^1	R^2	A	L	B	E	P
912	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_3$
913	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
914	Cl	X		$-NHCH_2CH_2-$	H	H	COC_4H_9
915	Cl	X		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
916	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
917	Cl	X		$-NHCH_2CH_2-$	H	H	H
918	Cl	X		$-NHCH_2CH_2-$	H	CH_3	H
919	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	H

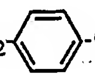
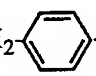
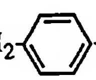
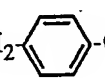
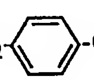
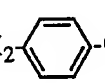
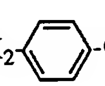
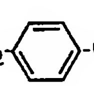
Ex.#	R^1	R^2	A	L	B	E	P
920	Cl	X			*	H	$COCH_3$
921	Cl	X			H	H	$COCH_2Cl$
922	Cl	X			H	H	COC_4H_9
923	Cl	X			H	CH_3	$COCH_3$
924	Cl	X			H	C_2H_5	$COCH_3$
925	Cl	X			*	H	H
926	Cl	X			H	CH_3	H

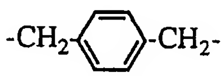
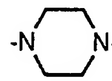
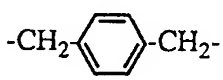
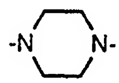
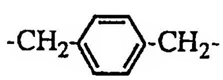
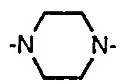
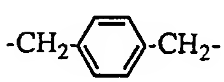
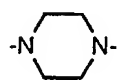
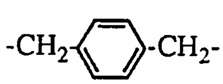
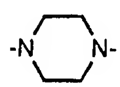
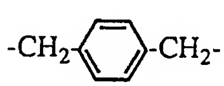
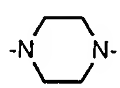
Ex.#	R^1	R^2	A	L	B	E	P
927	Cl	X			H	C_2H_5	H
928	Cl	X		-NH-	H	H	$COCH_3$
929	Cl	X		-NH-	H	H	$COCH_2Cl$
930	Cl	X		-NH-	H	H	COC_4H_9
931	Cl	X		-NH-	H	CH_3	$COCH_3$
932	Cl	X		-NH-	H	C_2H_5	$COCH_3$
933	Cl	X		-NH-	H	H	H
934	Cl	X		-NH-	H	CH_3	H

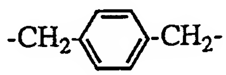
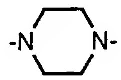
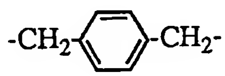
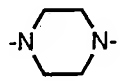
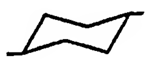
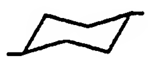
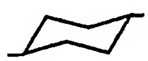
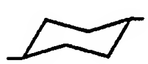
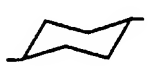
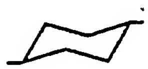
Ex.#	R^1	R^2	A	L	B	E	P
935	Cl	X	 $-CH_2-CH_2-$	-NH-	H	C_2H_5	H
936	Cl	X	 $-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	H	$COCH_3$
937	Cl	X	 $-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
938	Cl	X	 $-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	H	COC_4H_9
939	Cl	X	 $-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
940	Cl	X	 $-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
941	Cl	X	 $-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	H	H
942	Cl	X	 $-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	CH_3	H

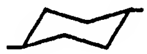
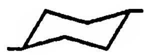
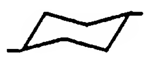
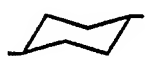
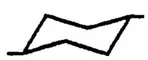
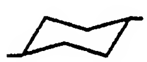
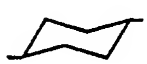
Ex.#	R^1	R^2	A	L	B	E	P
943	Cl	X		-NHCH2CH2-	H	C_2H_5	H
944	Cl	X			*	H	$COCH_3$
945	Cl	X			H	H	$COCH_2Cl$
946	Cl	X			H	H	COC_4H_9
947	Cl	X			H	CH_3	$COCH_3$
948	Cl	X			H	C_2H_5	$COCH_3$
949	Cl	X			*	H	H
950	Cl	X			H	CH_3	H

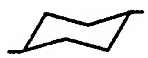
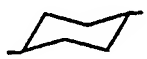
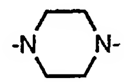
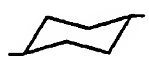
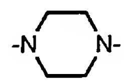
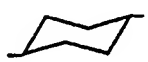
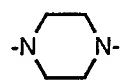
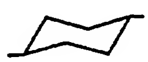
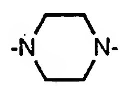
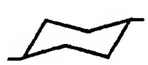
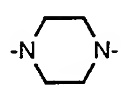
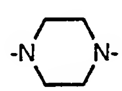
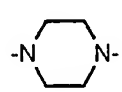
Ex.#	R^1	R^2	A	L	B	E	P
951	Cl	X			H	C_2H_5	H
952	Cl	X		-NH-	H	H	$COCH_3$
953	Cl	X		-NH-	H	H	$COCH_2Cl$
954	Cl	X		-NH-	H	H	COC_4H_9
955	Cl	X		-NH-	H	CH_3	$COCH_3$
956	Cl	X		-NH-	H	C_2H_5	$COCH_3$
957	Cl	X		-NH-	H	H	H
958	Cl	X		-NH-	H	CH_3	H

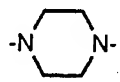
Ex.#	R^1	R^2	A	L	B	E	P
959	Cl	X	$-CH_2-$$-CH_2-$	-NH-	H	C_2H_5	H
960	Cl	X	$-CH_2-$$-CH_2-$	$-NHCH_2CH_2-$	H	H	$COCH_3$
961	Cl	X	$-CH_2-$$-CH_2-$	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
962	Cl	X	$-CH_2-$$-CH_2-$	$-NHCH_2CH_2-$	H	H	COC_4H_9
963	Cl	X	$-CH_2-$$-CH_2-$	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
964	Cl	X	$-CH_2-$$-CH_2-$	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
965	Cl	X	$-CH_2-$$-CH_2-$	$-NHCH_2CH_2-$	H	H	H
966	Cl	X	$-CH_2-$$-CH_2-$	$-NHCH_2CH_2-$	H	CH_3	H

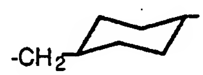
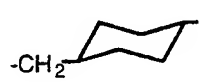
Ex.#	R^1	R^2	A	L	B	E	P
967	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	H
968	Cl	X			*	H	$COCH_3$
969	Cl	X			H	H	$COCH_2Cl$
970	Cl	X			H	H	COC_4H_9
971	Cl	X			H	CH_3	$COCH_3$
972	Cl	X			H	C_2H_5	$COCH_3$
973	Cl	X			*	H	H

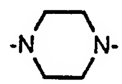
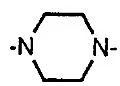
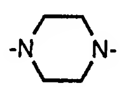
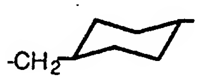
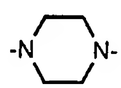
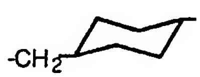
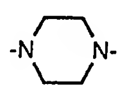
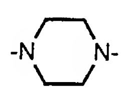
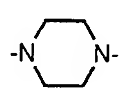
Ex.#	R^1	R^2	A	L	B	E	P
974	Cl	X			H	CH_3	H
975	Cl	X			H	C_2H_5	H
976	Cl	X		-NH-	H	H	$COCH_3$
977	Cl	X		-NH-	H	H	$COCH_2Cl$
978	Cl	X		-NH-	H	H	COC_4H_9
979	Cl	X		-NH-	H	CH_3	$COCH_3$
980	Cl	X		-NH-	H	C_2H_5	$COCH_3$
981	Cl	X		-NH-	H	H	H
982	Cl	X		-NH-	H	CH_3	H

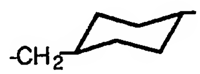
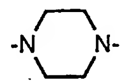
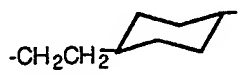
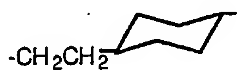
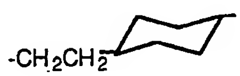
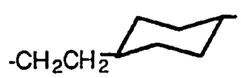
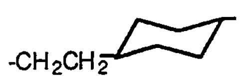
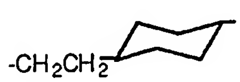
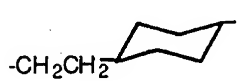
Ex.#	R^1	R^2	A	L	B	E	P
983	Cl	X		-NH-	H	C_2H_5	H
984	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_3$
985	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
986	Cl	X		$-NHCH_2CH_2-$	H	H	COC_4H_9
987	Cl	X		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
988	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
989	Cl	X		$-NHCH_2CH_2-$	H	H	H
990	Cl	X		$-NHCH_2CH_2-$	H	CH_3	H

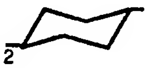
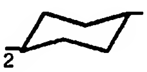
Ex.#	R^1	R^2	A	L	B	E	P
991	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	H
992	Cl	X			*	H	$COCH_3$
993	Cl	X			H	H	$COCH_2Cl$
994	Cl	X			H	H	COC_4H_9
995	Cl	X			H	CH_3	$COCH_3$
996	Cl	X			H	C_2H_5	$COCH_3$
997	Cl	X			*	H	H
998	Cl	X			H	CH_3	H

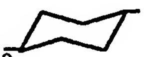
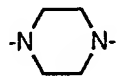
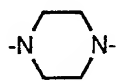
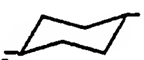
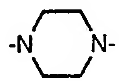
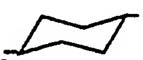
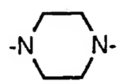
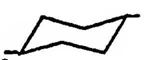
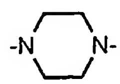
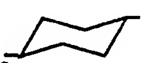
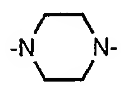
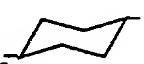
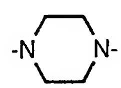
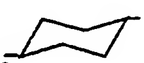
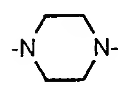
Ex.#	R^1	R^2	A	L	B	E	P
999	Cl	X			H	C_2H_5	H
1000	Cl	X		-NH-			H
1001	Cl	X		-NH-			H
1002	Cl	X		-NH-	H	H	COC_4H_9
1003	Cl	X		-NH-	H	CH_3	$COCH_3$
1004	Cl	X		-NH-	H	C_2H_5	$COCH_3$
1005	Cl	X		-NH-	H	H	H
1006	Cl	X		-NH-	H	CH_3	H

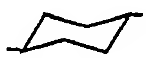
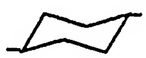
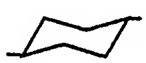
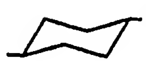
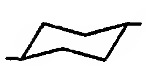
Ex.#	R^1	R^2	A	L	B	E	P
1007	Cl	X		-NH-	H	C_2H_5	H
1008	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_3$
1009	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1010	Cl	X		$-NHCH_2CH_2-$	H	H	COC_4H_9
1011	Cl	X		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1012	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1013	Cl	X		$-NHCH_2CH_2-$	H	H	H
1014	Cl	X		$-NHCH_2CH_2-$	H	CH_3	H

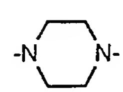
Ex.#	R^1	R^2	A	L	B	E	P
1015	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	H
1016	Cl	X			*	H	$COCH_3$
1017	Cl	X			H	H	$COCH_2Cl$
1018	Cl	X			H	H	COC_4H_9
1019	Cl	X			H	CH_3	$COCH_3$
1020	Cl	X			H	C_2H_5	$COCH_3$
1021	Cl	X			*	H	H
1022	Cl	X			H	CH_3	H

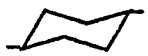
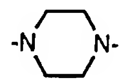
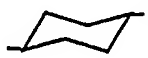
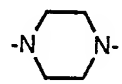
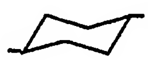
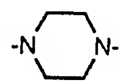
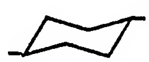
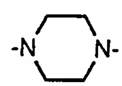
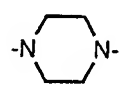
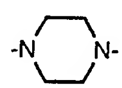
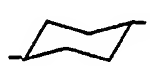
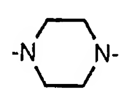
Ex.#	R^1	R^2	A	L	B	E	P
1023	Cl	X			H	C_2H_5	H
1024	Cl	X		-NH-	H	H	$COCH_3$
1025	Cl	X		-NH-	H	H	$COCH_2Cl$
1026	Cl	X		-NH-	H	H	COC_4H_9
1027	Cl	X		-NH-	H	CH_3	$COCH_3$
1028	Cl	X		-NH-	H	C_2H_5	$COCH_3$
1029	Cl	X		-NH-	H	H	H
1030	Cl	X		-NH-	H	CH_3	H

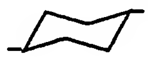
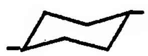
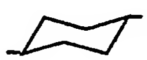
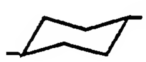
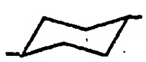
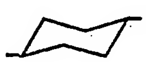
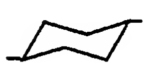
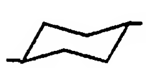
Ex.#	R¹	R²	A	L	B	E	P
1031	Cl	X	$-CH_2CH_2-$ 	-NH-	H	C_2H_5	H
1032	Cl	X	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	H	$COCH_3$
1033	Cl	X	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1034	Cl	X	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	H	COC_4H_9
1035	Cl	X	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1036	Cl	X	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1037	Cl	X	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	H	H
1038	Cl	X	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	CH_3	H
1039	Cl	X	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	C_2H_5	H

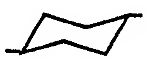
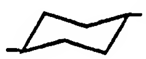
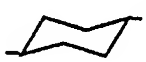
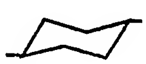
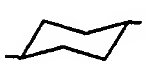
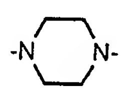
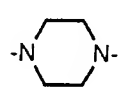
Ex.#	R1	R2	A	L	B	E	P
1040	Cl	X	$-CH_2CH_2-$ 		*	H	$COCH_3$
1041	Cl	X	$-CH_2CH_2-$ 		H	H	$COCH_2Cl$
1042	Cl	X	$-CH_2CH_2-$ 		H	H	COC_4H_9
1043	Cl	X	$-CH_2CH_2-$ 		H	CH_3	$COCH_3$
1044	Cl	X	$-CH_2CH_2-$ 		H	C_2H_5	$COCH_3$
1045	Cl	X	$-CH_2CH_2-$ 		*	H	H
1046	Cl	X	$-CH_2CH_2-$ 		H	CH_3	H
1047	Cl	X	$-CH_2CH_2-$ 		H	C_2H_5	H

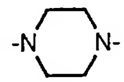
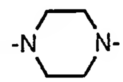
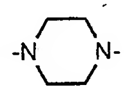
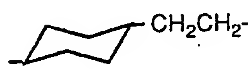
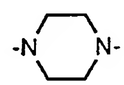
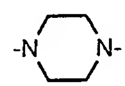
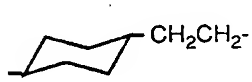
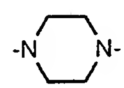
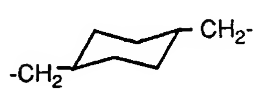
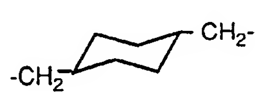
Ex.#	R^1	R^2	A	L	B	E	P
1048	Cl	X	 CH_2-	-NH-	H	H	$COCH_3$
1049	Cl	X	 CH_2-	-NH-	H	H	$COCH_2Cl$
1050	Cl	X	 CH_2-	-NH-	H	H	COC_4H_9
1051	Cl	X	 CH_2-	-NH-	H	CH_3	$COCH_3$
1052	Cl	X	 CH_2-	-NH-	H	C_2H_5	$COCH_3$
1053	Cl	X	 CH_2-	-NH-	H	H	H
1054	Cl	X	 CH_2-	-NH-	H	CH_3	H
1055	Cl	X	 CH_2-	-NH-	H	C_2H_5	H

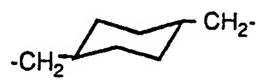
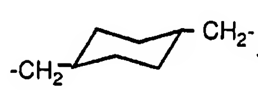
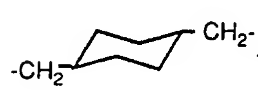
Ex.#	R^1	R^2	A	L	B	E	P
1056	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_3$
1057	Cl	X		-NH-	H	H	$COCH_2Cl$
1058	Cl	X		-NH-	H	H	COC_4H_9
1059	Cl	X		-NH-	H	CH_3	$COCH_3$
1060	Cl	X		-NH-	H	C_2H_5	$COCH_3$
1061	Cl	X		$-NHCH_2CH_2-$	H	H	H
1062	Cl	X		$-NHCH_2CH_2-$	H	CH_3	H
1063	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	H
1064	Cl	X			*	H	$COCH_3$

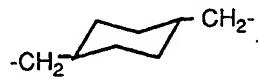
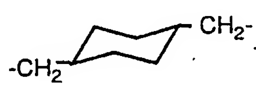
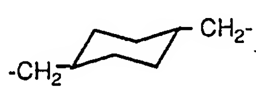
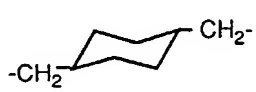
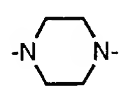
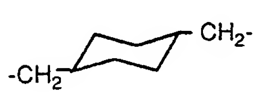
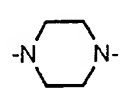
Ex.#	R1	R2	A	L	B	E	P
1065	Cl	X	 CH_2-		H	H	$COCH_2Cl$
1066	Cl	X	 CH_2-		H	H	COC_4H_9
1067	Cl	X	 CH_2-		H	CH_3	$COCH_3$
1068	Cl	X	 CH_2-		C_2H_5		COC[illegible]
1069	Cl	X	 CH_2-		*	H	H
1070	Cl	X	 CH_2-		H	CH_3	H
1071	Cl	X	 CH_2-		H	C_2H_5	H
1072	Cl	X	 CH_2CH_2-	-NH-	H	H	$COCH_3$

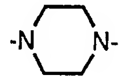
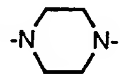
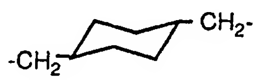
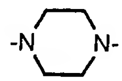
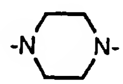
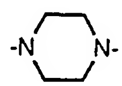
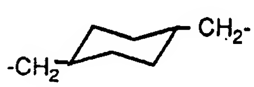
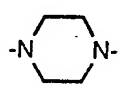
Ex.#	R1	R2	A	L	B	E	P
1073	Cl	X	 CH_2CH_2-	-NH-	H	H	$COCH_2Cl$
1074	Cl	X	 CH_2CH_2-	-NH-	H	H	COC_4H_9
1075	Cl	X	 CH_2CH_2-	-NH-	H	CH_3	$COCH_3$
1076	Cl	X	 CH_2CH_2-	-NH-	H	C_2H_5	$COCH_3$
1077	Cl	X	 CH_2CH_2-	-NH-	H	H	H
1078	Cl	X	 CH_2CH_2-	-NH-	H	CH_3	H
1079	Cl	X	 CH_2CH_2-	-NH-	H	C_2H_5	H
1080	Cl	X	 CH_2CH_2-	$-NHCH_2CH_2-$	H	H	$COCH_3$
1081	Cl	X	 CH_2CH_2-	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$

Ex.#	R^1	R^2	A	L	B	E	P
1082	Cl	X	 CH_2CH_2-	$-NHCH_2CH_2-$	H	H	COC_4H_9
1083	Cl	X	 CH_2CH_2-	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1084	Cl	X	 CH_2CH_2-	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1085	Cl	X	 CH_2CH_2-	$-NHCH_2CH_2-$	H	H	H
1086	Cl	X	 CH_2CH_2-	$-NHCH_2CH_2-$	H	CH_3	H
1087	Cl	X	 CH_2CH_2-	$-NHCH_2CH_2-$	H	C_2H_5	H
1088	Cl	X	 CH_2CH_2-		*	H	$COCH_3$
1089	Cl	X	 CH_2CH_2-		H	H	$COCH_2Cl$

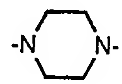
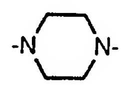
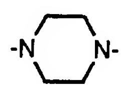
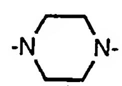
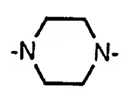
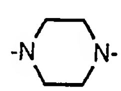
Ex.#	R1	R2	A	L	B	E	P
1090	Cl	X			H	H	COC_4H_9
1091	Cl	X			H	CH_3	$COCH_3$
1092	Cl	X			H	C_2H_5	$COCH_3$
1093	Cl	X			*	H	H
1094	Cl	X			H	CH_3	H
1095	Cl	X			H	C_2H_5	H
1096	Cl	X		–NH–	H	H	$COCH_3$
1097	Cl	X		–NH–	H	H	$COCH_2Cl$

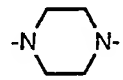
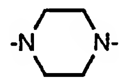
Ex.#	R^1	R^2	A	L	B	E	P
1098	Cl	X		-NH-	H	H	COC_4H_9
1099	Cl	X		-NH-	H	CH_3	$COCH_3$
1100	Cl	X		-NH-	H	C_2H_5	$COCH_3$
1101	Cl	X		-NH-	H	H	H
1102	Cl	X		-NH-	H	CH_3	H
1103	Cl	X		-NH-	H	C_2H_5	H
1104	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_3$
1105	Cl	X		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$

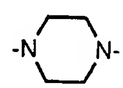
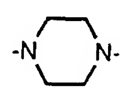
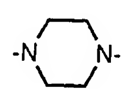
Ex.#	R^1	R^2	A	L	B	E	P
1106	Cl	X		$-NHCH_2CH_2-$	H	H	COC_4H_9
1107	Cl	X		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1108	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1109	Cl	X		$-NHCH_2CH_2-$	H	H	H
1110	Cl	X		$-NHCH_2CH_2-$	H	CH_3	H
1111	Cl	X		$-NHCH_2CH_2-$	H	C_2H_5	H
1112	Cl	X			*	H	$COCH_3$
1113	Cl	X			H	H	$COCH_2Cl$

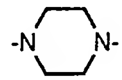
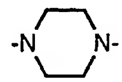
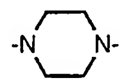
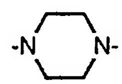
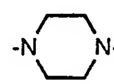
Ex.#	R^1	R^2	A	L	B	E	P
114	Cl	X			H	H	COC_4H_9
1115	Cl	X			H	CH_3	$COCH_3$
1116	Cl	X			H	C_2H_5	$COCH_3$
1117	Cl	X			*	H	H
1118	Cl	X			H	CH_3	H
1119	Cl	X			H	C_2H_5	H
1120	X	Cl	single bond	-NH-	H	H	$COCH_3$
1121	X	Cl	single bond	-NH-	H	H	$COCH_2Cl$
1122	X	Cl	single bond	-NH-	H	H	COC_4H_9

Ex.#	R^1	R^2	A	L	B	E	P
1123	X	Cl	single bond	-NH-	H	CH_3	$COCH_3$
1124	X	Cl	single bond	-NH-	H	C_2H_5	$COCH_3$
1125	X	Cl	single bond	-NH-	H	H	H
1126	X	Cl	single bond	-NH-	H	CH_3	H
1127	X	Cl	single bond	-NH-	H	C_2H_5	H
1128	X	Cl	single bond	$-NHCH_2CH_2-$	H	H	$COCH_3$
1129	X	Cl	single bond	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1130	X	Cl	single bond	$-NHCH_2CH_2-$	H	H	COC_4H_9
1131	X	Cl	single bond	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1132	X	Cl	single bond	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1133	X	Cl	single bond	$-NHCH_2CH_2-$	H	H	H
1134	X	Cl	single bond	$-NHCH_2CH_2-$	H	CH_3	H

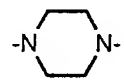
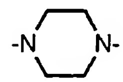
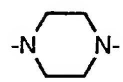
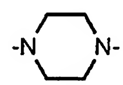
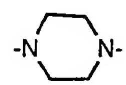
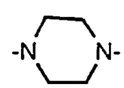
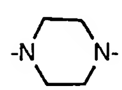
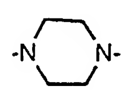
Ex.#	R1	R2	A	L	B	E	P
1135	X	Cl	single bond	$-NHCH_2CH_2-$	H	C_2H_5	H
1136	X	Cl	single bond		*	H	$COCH_3$
1137	X	Cl	single bond		H	H	$COCH_2Cl$
1138	X	Cl	single bond		H	H	COC_4H_9
1139	X	Cl	single bond		H	CH_3	$COCH_3$
1140	X	Cl	single bond		H	C_2H_5	$COCH_3$
1141	X	Cl	single bond		*	H	H

Ex.#	R^1	R^2	A	L	B	E	P
1142	X	Cl	single bond		H	CH_3	H
1143	X	Cl	single bond		H	C_2H_5	H
1144	X	Cl	CH_2	-NH-	H	H	$COCH_2Cl$
1145	X	Cl	CH_2	-NH-	H	H	COC_4H_9
1146	X	Cl	CH_2	-NH-	H	CH_3	$COCH_3$
1147	X	Cl	CH_2	-NH-	H	C_2H_5	$COCH_3$
1148	X	Cl	CH_2	-NH-	H	H	H
1149	X	Cl	CH_2	-NH-	H	CH_3	H
1150	X	Cl	CH_2	-NH-	H	C_2H_5	H
1151	X	Cl	CH_2	$-NHCH_2CH_2-$	H	H	$COCH_3$
1152	X	Cl	CH_2	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$

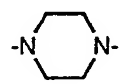
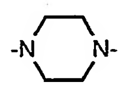
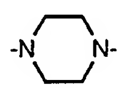
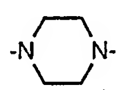
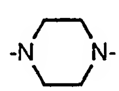
Ex.#	R^1	R^2	A	L	B	E	P
1153	X	Cl	CH_2	$-NHCH_2CH_2-$	H	H	COC_4H_9
1154	X	Cl	CH_2	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1155	X	Cl	CH_2	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1156	X	Cl	CH_2	$-NHCH_2CH_2-$	H	H	H
1157	X	Cl	CH_2	$-NHCH_2CH_2-$	H	CH_3	H
1158	X	Cl	CH_2	$-NHCH_2CH_2-$	H	C_2H_5	H
1159	X	Cl	CH_2		*	H	$COCH_3$
1160	X	Cl	CH_2		H	H	$COCH_2Cl$
1161	X	Cl	CH_2		H	H	COC_4H_9

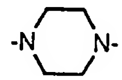
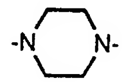
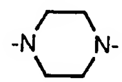
Ex.#	R^1	R^2	A	L	B	E	P
1162	X	Cl	CH_2		H	CH_3	$COCH_3$
1163	X	Cl	CH_2		H	C_2H_5	$COCH_3$
1164	X	Cl	CH_2		*	H	H
1165	X	Cl	CH_2		H	CH_3	H
1166	X	Cl	CH_2		H	C_2H_5	H
1167	X	Cl	CH_2CH_2	-NH-	H	H	$COCH_3$
1168	X	Cl	CH_2CH_2	-NH-	H	H	$COCH_2Cl$
1169	X	Cl	CH_2CH_2	-NH-	H	H	COC_4H_9
1170	X	Cl	CH_2CH_2	-NH-	H	CH_3	$COCH_3$

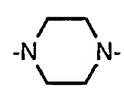
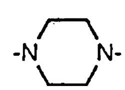
Ex.#	R^1	R^2	A	L	B	E	P
1171	X	Cl	CH_2CH_2	-NH-	H	C_2H_5	$COCH_3$
1172	X	Cl	CH_2CH_2	-NH-	H	H	H
1173	X	Cl	CH_2CH_2	-NH-	H	CH_3	H
1174	X	Cl	CH_2CH_2	-NH-	H	C_2H_5	H
1175	X	Cl	CH_2CH_2	$-NHCH_2CH_2-$	H	H	$COCH_3$
1176	X	Cl	CH_2CH_2	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1177	X	Cl	CH_2CH_2	$-NHCH_2CH_2-$	H	H	COC_4H_9
1178	X	Cl	CH_2CH_2	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1179	X	Cl	CH_2CH_2	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1180	X	Cl	CH_2CH_2	$-NHCH_2CH_2-$	H	H	H
1181	X	Cl	CH_2CH_2	$-NHCH_2CH_2-$	H	CH_3	H
1182	X	Cl	CH_2CH_2	$-NHCH_2CH_2-$	H	C_2H_5	H

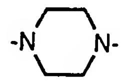
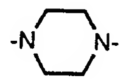
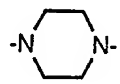
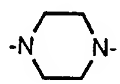
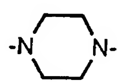
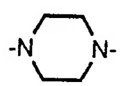
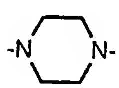
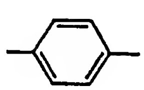
Ex.#	R^1	R^2	A	L	B	E	P
1183	X	Cl	CH_2CH_2		*	H	$COCH_3$
1184	X	Cl	CH_2CH_2		H	H	$COCH_2Cl$
1185	X	Cl	CH_2CH_2		H	H	COC_4H_9
1186	X	Cl	CH_2CH_2		H	CH_3	$COCH_3$
1187	X	Cl	CH_2CH_2		H	C_2H_5	$COCH_3$
1188	X	Cl	CH_2CH_2		*	H	H
1189	X	Cl	CH_2CH_2		H	CH_3	H
1190	X	Cl	CH_2CH_2		H	C_2H_5	H

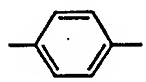
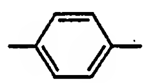
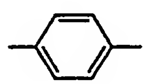
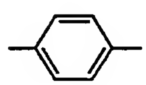
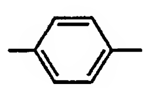
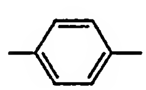
Ex.#	R^1	R^2	A	L	B	E	P
1191	X	Cl	C_3H_6 (n)	-NH-	H	H	$COCH_3$
1192	X	Cl	C_3H_6 (n)	-NH-	H	H	$COCH_2Cl$
1193	X	Cl	C_3H_6 (n)	-NH-	H	H	COC_4H_9
1194	X	Cl	C_3H_6 (n)	-NH-	H	CH_3	$COCH_3$
1195	X	Cl	C_3H_6 (n)	-NH-	H	C_2H_5	$COCH_3$
1196	X	Cl	C_3H_6 (n)	-NH-	H	H	H
1197	X	Cl	C_3H_6 (n)	-NH-	H	CH_3	H
1198	X	Cl	C_3H_6 (n)	-`IH-	H	C_2H_5	H
1199	X	Cl	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	$COCH_3$
1200	X	Cl	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1201	X	Cl	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	COC_4H_9
1202	X	Cl	C_3H_6 (n)	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$

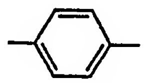
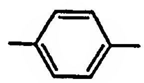
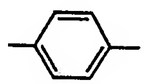
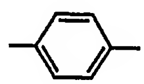
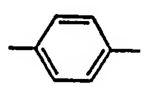
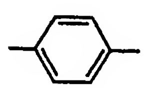
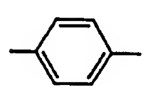
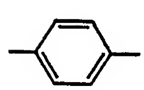
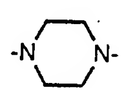
Ex.#	R^1	R^2	A	L	B	E	P
1203	X	Cl	C_3H_6 (n)	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1204	X	Cl	C_3H_6 (n)	$-NHCH_2CH_2-$	H	H	H
1205	X	Cl	C_3H_6 (n)	$-NHCH_2CH_2-$	H	CH_3	H
1206	X	Cl	C_3H_6 (n)	$-NHCH_2CH_2-$	H	C_2H_5	H
1207	X	Cl	C_3H_6 (n)		*	H	$COCH_3$
1208	X	Cl	C_3H_6 (n)		H	H	$COCH_2Cl$
1209	X	Cl	C_3H_6 (n)		H	H	COC_4H_9
1210	X	Cl	C_3H_6 (n)		H	CH_3	$COCH_3$
1211	X	Cl	C_3H_6 (n)		H	C_2H_5	$COCH_3$

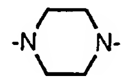
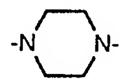
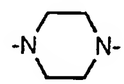
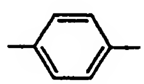
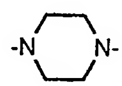
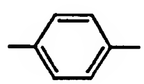
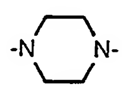
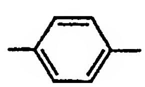
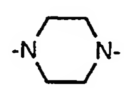
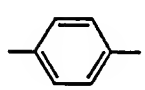
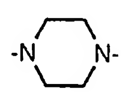
Ex.#	R^1	R^2	A	L	B	E	P
1212	X	Cl	C_3H_6 (n)		*	H	H
1213	X	Cl	C_3H_6 (n)		H	CH_3	H
1214	X	Cl	C_3H_6 (n)		H	C_2H_5	H
1215	X	Cl	C_4H_8 (n)	-NH-	H	H	$COCH_3$
1216	X	Cl	C_4H_8 (n)	-NH-	H	H	$COCH_2Cl$
1217	X	Cl	C_4H_8 (n)	-NH-	H	H	COC_4H_9
1218	X	Cl	C_4H_8 (n)	-NH-	H	CH_3	$COCH_3$
1219	CX	Cl	C_4H_8 (n)	-NH-	H	C_2H_5	$COCH_3$
1220	X	Cl	C_4H_8 (n)	-NH-	H	H	H
1221	X	Cl	C_4H_8 (n)	-NH-	H	CH_3	H

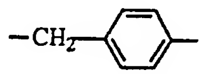
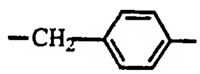
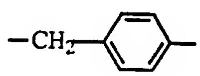
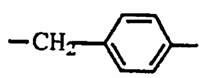
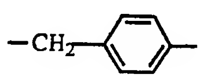
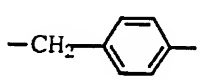
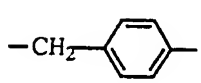
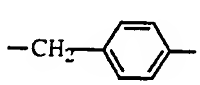
Ex.#	R^1	R^2	A	L	B	E	P
1222	X	Cl	C_4H_8 (n)	-NH-	H	C_2H_5	H
1223	X	Cl	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	$COCH_3$
1224	X	Cl	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1225	X	Cl	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	COC_4H_9
1226	X	Cl	C_4H_8 (n)	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1227	X	Cl	C_4H_8 (n)	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1228	X	Cl	C_4H_8 (n)	$-NHCH_2CH_2-$	H	H	H
1229	X	Cl	C_4H_8 (n)	$-NHCH_2CH_2-$	H	CH_3	H
1230	X	Cl	C_4H_8 (n)	$-NHCH_2CH_2-$	H	C_2H_5	H
1231	X	Cl	C_4H_8 (n)		*	H	$COCH_3$
1232	X	Cl	C_4H_8 (n)		H	H	$COCH_2Cl$

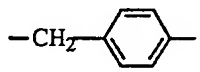
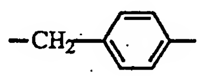
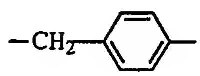
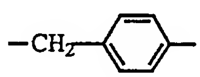
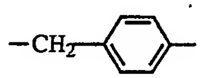
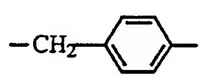
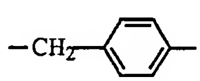
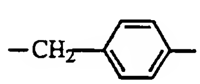
Ex.#	R^1	R^2	A	L	B	E	P
1233	X	Cl	C_4H_8 (n)		H	H	COC_4H_9
1234	X	Cl	C_4H_8 (n)		H	CH_3	$COCH_3$
1235	X	Cl	C_4H_8 (n)		H	C_2H_5	$COCH_3$
1236	X	Cl	C_4H_8 (n)		*	H	H
1237	X	Cl	C_4H_8 (n)		H	CH_3	H
1238	X	Cl	C_4H_8 (n)		H	C_2H_5	H
1239	X	Cl		-NH-	H	H	$COCH_3$
1240	X	Cl		-NH-	H	H	$COCH_2Cl$

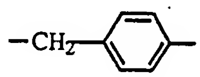
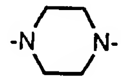
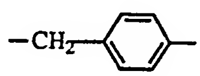
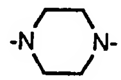
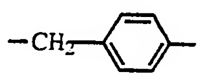
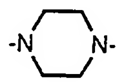
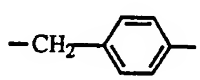
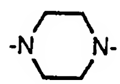
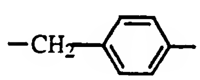
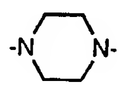
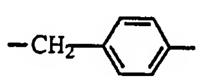
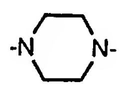
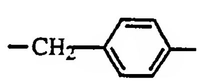
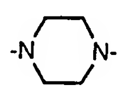
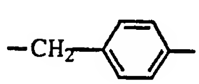
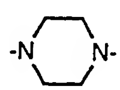
Ex.#	R^1	R^2	A	L	B	E	P
1241	X	Cl		-NH-	H	H	COC_4H_9
1242	X	Cl		-NH-	H	CH_3	$COCH_3$
1243	X	Cl		-NH-	H	C_2H_5	$COCH_3$
1244	X	Cl		-NH-	H	H	H
1245	X	Cl		-NH-	H	CH_3	H
1246	X	Cl		-NH-	H	C_2H_5	H
1247	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_3$

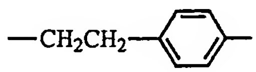
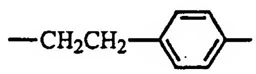
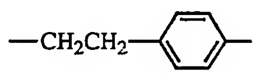
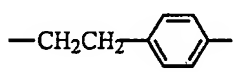
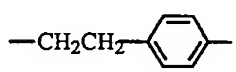
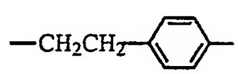
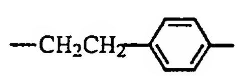
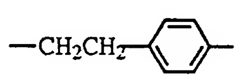
Ex.#	R^1	R^2	A	L	B	E	P
1248	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1249	X	Cl		$-NHCH_2CH_2-$	H	H	COC_4H_9
1250	X	Cl		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1251	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1252	X	Cl		$-NHCH_2CH_2-$	H	H	H
1253	X	Cl		$-NHCH_2CH_2-$	H	CH_3	H
1254	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	H
1255	X	Cl			*	H	$COCH_3$

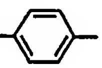
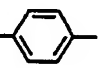
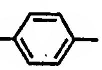
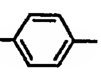
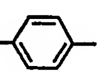
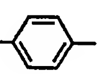
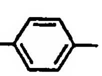
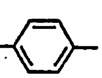
Ex.#	R^1	R^2	A	L	B	E	P
1256	X	Cl			H	H	$COCH_2Cl$
1257	X	Cl			H	H	COC_4H_9
1258	X	Cl			H	CH_3	$COCH_3$
1259	X	Cl			H	C_2H_5	$COCH_3$
1260	X	Cl			*	H	H
1261	X	Cl			H	CH_3	H
1262	X	Cl			H	C_2H_5	H

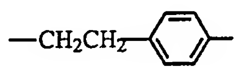
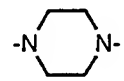
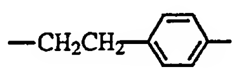
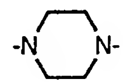
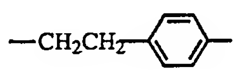
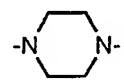
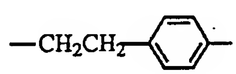
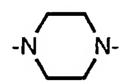
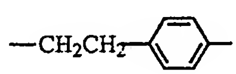
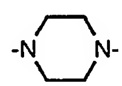
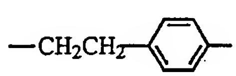
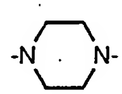
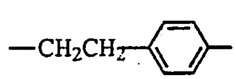
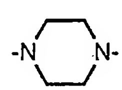
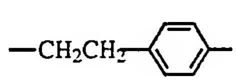
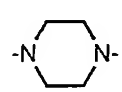
Ex.#	R^1	R^2	A	L	B	E	P
1263	X	Cl		-NH-	H	H	$COCH_3$
1264	X	Cl		-NH-	H	H	$COCH_2Cl$
1265	X	Cl		-NH-	H	H	COC_4H_9
1266	X	Cl		-NH-	H	CH_3	$COCH_3$
1267	X	Cl		-NH-	H	C_2H_5	$COCH_3$
1268	X	Cl		-NH-	H	H	H
1269	X	Cl		-NH-	H	CH_3	H
1270	X	Cl		-NH-	H	C_2H_5	H

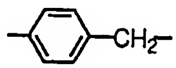
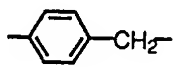
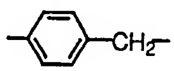
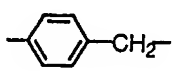
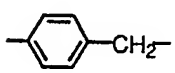
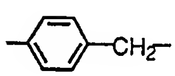
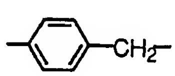
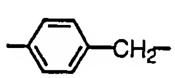
Ex.#	R^1	R^2	A	L	B	E	P
1271	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_3$
1272	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1273	X	Cl		$-NHCH_2CH_2-$	H	H	COC_4H_9
1274	X	Cl		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1275	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1276	X	Cl		$-NHCH_2CH_2-$	H	H	H
1277	X	Cl		$-NHCH_2CH_2-$	H	CH_3	H
1278	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	H

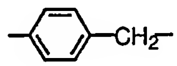
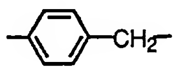
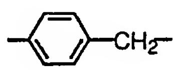
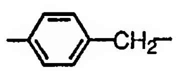
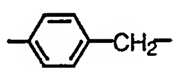
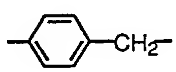
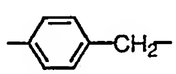
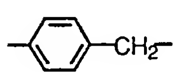
Ex.#	R1	R2	A	L	B	E	P
1279	X	Cl			*	H	$COCH_3$
1280	X	Cl			H	H	$COCH_2Cl$
1281	X	Cl			H	H	COC_4H_9
1282	X	Cl			H	CH_3	$COCH_3$
1283	X	Cl			H	C_2H_5	$COCH_3$
1284	X	Cl			*	H	H
1285	X	Cl			H	CH_3	H
1286	X	Cl			H	C_2H_5	H

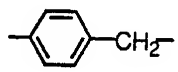
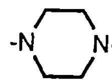
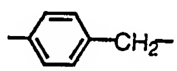
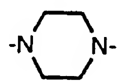
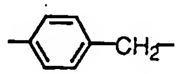
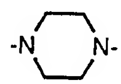
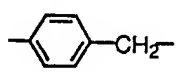
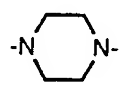
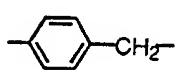
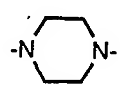
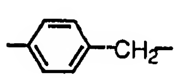
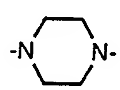
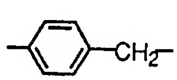
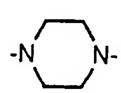
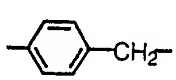
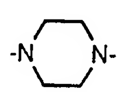
Ex.#	R^1	R^2	A	L	B	E	P
1287	X	Cl		-NH-	H	H	$COCH_3$
1288	X	Cl		-NH-	H	H	$COCH_2Cl$
1289	X	Cl		-NH-	H	H	COC_4H_9
1290	X	Cl		-NH-	H	CH_3	$COCH_3$
1291	X	Cl		-NH-	H	C_2H_5	$COCH_3$
1292	X	Cl		-NH-	H	H	H
1293	X	Cl		-NH-	H	CH_3	H
1294	X	Cl		-NH-	H	C_2H_5	H

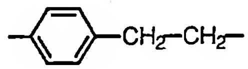
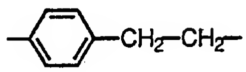
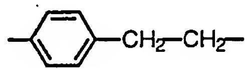
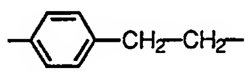
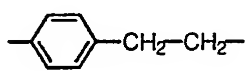
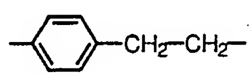
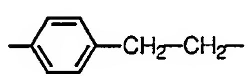
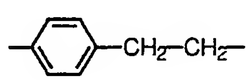
Ex.#	R^1	R^2	A	L	B	E	P
1295	X	Cl	$-CH_2CH_2-$	$-NHCH_2CH_2-$	H	H	$COCH_3$
1296	X	Cl	$-CH_2CH_2-$	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1297	X	Cl	$-CH_2CH_2-$	$-NHCH_2CH_2-$	H	H	COC_4H_9
1298	X	Cl	$-CH_2CH_2-$	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1299	X	Cl	$-CH_2CH_2-$	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1300	X	Cl	$-CH_2CH_2-$	$-NHCH_2CH_2-$	H	H	H
1301	X	Cl	$-CH_2CH_2-$	$-NHCH_2CH_2-$	H	CH_3	H
1302	X	Cl	$-CH_2CH_2-$	$-NHCH_2CH_2-$	H	C_2H_5	H

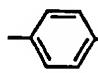
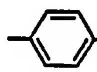
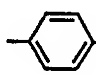
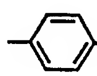
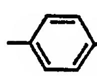
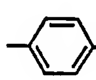
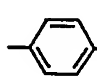
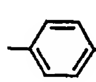
Ex.#	R1	R2	A	L	B	E	P
1303	X	Cl			*	H	$COCH_3$
1304	X	Cl			H	H	$COCH_2Cl$
1305	X	Cl			H	H	COC_4H_9
1306	X	Cl			H	CH_3	$COCH_3$
1307	X	Cl			H	C_2H_5	$COCH_3$
1308	X	Cl			*	H	H
1309	X	Cl			H	CH_3	H
1310	X	Cl			H	C_2H_5	H

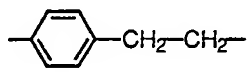
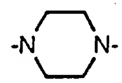
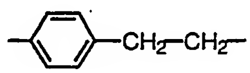
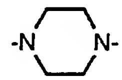
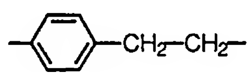
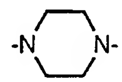
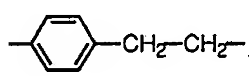
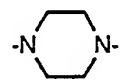
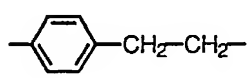
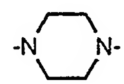
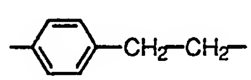
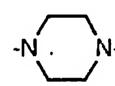
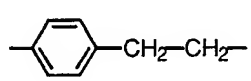
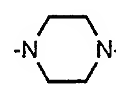
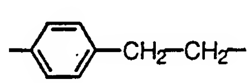
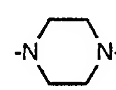
Ex.#	R^1	R^2	A	L	B	E	P
1311	X	Cl		-NH-	H	H	$COCH_3$
1312	X	Cl		-NH-	H	H	$COCH_2Cl$
1313	X	Cl		-NH-	H	H	COC_4H_9
1314	X	Cl		-NH-	H	CH_3	$COCH_3$
1315	X	Cl		-NH-	H	C_2H_5	$COCH_3$
1316	X	Cl		-NH-	H	H	H
1317	X	Cl		-NH-	H	CH_3	H
1318	X	Cl		-NH-	H	C_2H_5	H

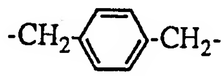
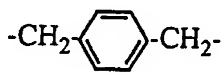
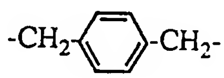
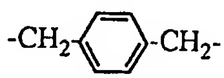
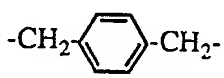
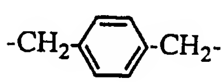
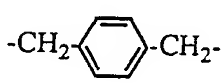
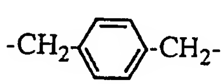
Ex.#	R^1	R^2	A	L	B	E	P
1319	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_3$
1320	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1321	X	Cl		$-NHCH_2CH_2-$	H	H	COC_4H_9
1322	X	Cl		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1323	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1324	X	Cl		$-NHCH_2CH_2-$	H	H	H
1325	X	Cl		$-NHCH_2CH_2-$	H	CH_3	H
1326	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	H

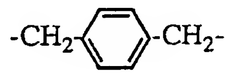
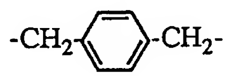
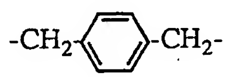
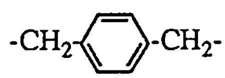
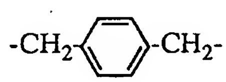
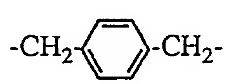
Ex.#	R1	R2	A	L	B	E	P
1327	X	Cl			*	H	$COCH_3$
1328	X	Cl			H	H	$COCH_2Cl$
1329	X	Cl			H	H	COC_4H_9
1330	X	Cl			H	CH_3	$COCH_3$
1331	X	Cl			H	C_2H_5	$COCH_3$
1332	X	Cl			*	H	H
1333	X	Cl			H	CH_3	H
1334	X	Cl			H	C_2H_5	H

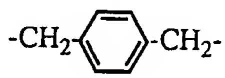
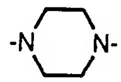
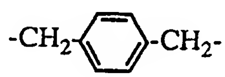
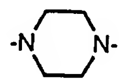
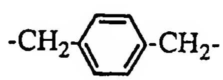
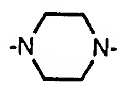
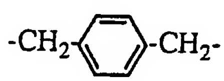
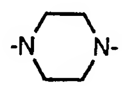
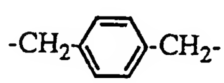
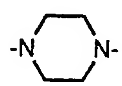
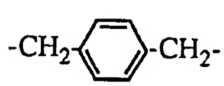
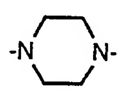
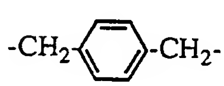
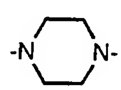
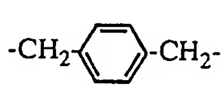
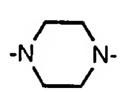
Ex.#	R^1	R^2	A	L	B	E	P
1335	X	Cl		-NH-	H	H	$COCH_3$
1336	X	Cl		-NH-	H	H	$COCH_2Cl$
1337	X	Cl		-NH-	H	H	COC_4H_9
1338	X	Cl		-NH-	H	CH_3	$COCH_3$
1339	X	Cl		-NH-	H	C_2H_5	$COCH_3$
1340	X	Cl		-NH-	H	H	H
1341	X	Cl		-NH-	H	CH_3	H
1342	X	Cl		-NH-	H	C_2H_5	H

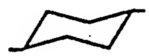
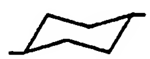
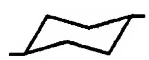
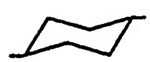
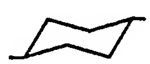
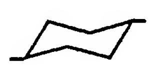
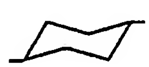
Ex.#	R^1	R^2	A	L	B	E	P
1343	X	Cl	$-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	H	$COCH_3$
1344	X	Cl	$-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1345	X	Cl	$-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	H	COC_4H_9
1346	X	Cl	$-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1347	X	Cl	$-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1348	X	Cl	$-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	H	H
1349	X	Cl	$-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	CH_3	H
1350	X	Cl	$-CH_2-CH_2-$	$-NHCH_2CH_2-$	H	C_2H_5	H

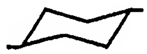
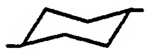
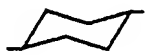
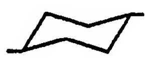
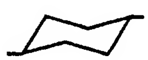
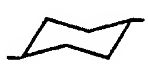
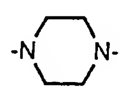
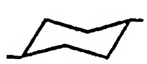
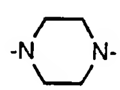
Ex.#	R1	R2	A	L	B	E	P
1351	X	Cl			*	H	$COCH_3$
1352	X	Cl			H	H	$COCH_2Cl$
1353	X	Cl			H	H	COC_4H_9
1354	X	Cl			H	CH_3	$COCH_3$
1355	X	Cl			H	C_2H_5	$COCH_3$
1356	X	Cl			*	H	H
1357	X	Cl			H	CH_3	H
1358	X	Cl			H	C_2H_5	H

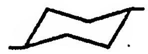
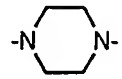
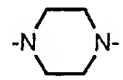
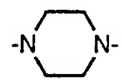
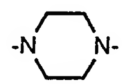
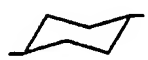
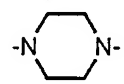
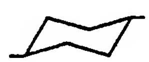
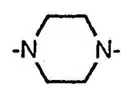
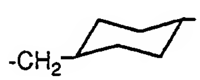
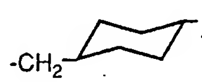
Ex.#	R¹	R²	A	L	B	E	P
1359	X	Cl		-NH-	H	H	$COCH_3$
1360	X	Cl		NH-	H	H	$COCH_2Cl$
1361	X	Cl		-NH-	H	H	COC_4H_9
1362	X	Cl		-NH-	H	CH_3	$COCH_3$
1363	X	Cl		-NH-	H	C_2H_5	$COCH_3$
1364	X	Cl		-NH-	H	H	H
1365	X	Cl		-NH-	H	CH_3	H
1366	X	Cl		-NH-	H	C_2H_5	H

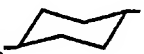
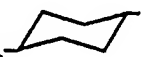
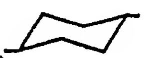
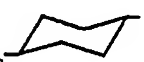
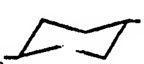
Ex.#	R^1	R^2	A	L	B	E	P
1367	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_3$
1368	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1369	X	Cl		$-NHCH_2CH_2-$	H	H	COC_4H_9
1370	X	Cl		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1371	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1372	X	Cl		$-NHCH_2CH_2-$	H	H	H
1373	X	Cl		$-NHCH_2CH_2-$	H	CH_3	H
1374	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	H

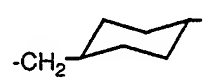
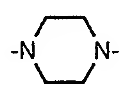
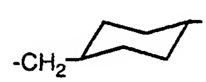
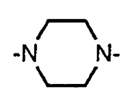
Ex.#	R^1	R^2	A	L	B	E	P
1375	X	Cl			*	H	$COCH_3$
1376	X	Cl			H	H	$COCH_2Cl$
1377	X	Cl			H	H	COC_4H_9
1378	X	Cl			H	CH_3	$COCH_3$
1379	X	Cl			H	C_2H_5	$COCH_3$
1380	X	Cl			*	H	H
1381	X	Cl			H	CH_3	H
1382	X	Cl			H	C_2H_5	H

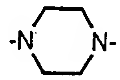
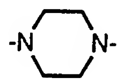
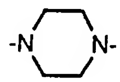
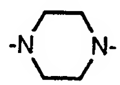
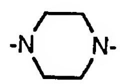
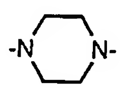
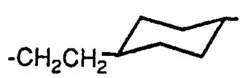
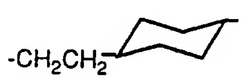
Ex.#	R^1	R^2	A	L	B	E	P
1383	X	Cl		-NH-	H	H	$COCH_3$
1384	X	Cl		-NH-	H	H	$COCH_2Cl$
1385	X	Cl		-NH-	H	H	COC_4H_9
1386	X	Cl		-NH-	H	CH_3	$COCH_3$
1387	X	Cl		-NH-	H	C_2H_5	$COCH_3$
1388	X	Cl		-NH-	H	H	H
1389	X	Cl		-NH-	H	CH_3	H
1390	X	Cl		-NH-	H	C_2H_5	H
1391	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_3$

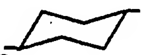
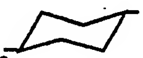
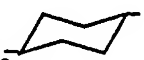
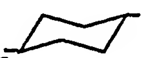
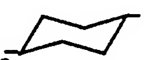
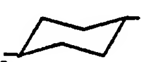
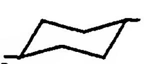
Ex.#	R1	R2	A	L	B	E	P
1392	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1393	X	Cl		$-NHCH_2CH_2-$	H	H	COC_4H_9
1394	X	Cl		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1395	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1396	X	Cl		$-NHCH_2CH_2-$	H	H	H
1397	X	Cl		$-NHCH_2CH_2-$	H	CH_3	H
1398	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	H
1399	X	Cl			*	H	$COCH_3$
1400	X	Cl			H	H	$COCH_2Cl$

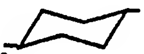
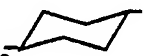
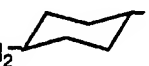
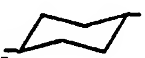
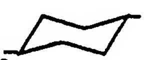
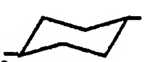
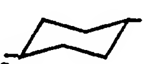
Ex.#	R1	R2	A	L	B	E	P
1401	X	Cl			H	H	COC_4H_9
1402	X	Cl			H	CH_3	$COCH_3$
1403	X	Cl			H	C_2H_5	$COCH_3$
1404	X	Cl			*	H	H
1405	X	Cl			H	CH_3	H
1406	X	Cl			H	C_2H_5	H
1407	X	Cl		-NH-	H	H	$COCH_3$
1408	X	Cl		-NH-	H	H	$COCH_2Cl$

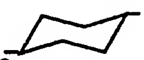
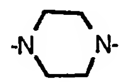
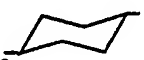
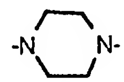
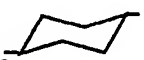
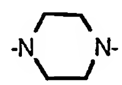
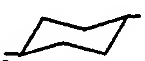
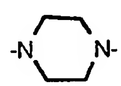
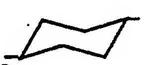
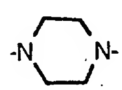
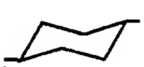
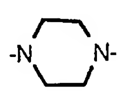
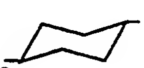
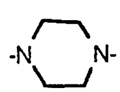
Ex.#	R1	R2	A	L	B	E	P
1409	X	Cl	$-CH_2-$ 	-NH-	H	H	COC_4H_9
1410	X	Cl	$-CH_2-$ 	-NH-	H	CH_3	$COCH_3$
1411	X	Cl	$-CH_2-$ 	-NH-	H	C_2H_5	$COCH_3$
1412	X	Cl	$-CH_2-$ 	-NH-	H	H	H
1413	X	Cl	$-CH_2-$ 	-NH-	H	CH_3	H
1414	X	Cl	$-CH_2-$ 	-NH-	H	C_2H_5	H
1415	X	Cl	$-CH_2-$ 	$-NHCH_2CH_2-$	H	H	$COCH_3$
1416	X	Cl	$-CH_2-$ 	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$

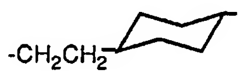
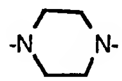
Ex.#	R^1	R^2	A	L	B	E	P
1417	X	Cl		$-NHCH_2CH_2-$	H	H	COC_4H_9
1418	X	Cl		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1419	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1420	X	Cl		$-NHCH_2CH_2-$	H	H	H
1421	X	Cl		$-NHCH_2CH_2-$	H	CH_3	H
1422	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	H
1423	X	Cl			*	H	$COCH_3$
1424	X	Cl			H	H	$COCH_2Cl$

Ex.#	R1	R2	A	L	B	E	P
1425	X	Cl			H	H	COC_4H_9
1426	X	Cl			H	CH_3	$COCH_3$
1427	X	Cl			H	C_2H_5	$COCH_3$
1428	X	Cl			*	H	H
1429	X	Cl			H	CH_3	H
1430	X	Cl			H	C_2H_5	H
1431	X	Cl		-NH-	H	H	$COCH_3$
1432	X	Cl		-NH-	H	H	$COCH_2Cl$

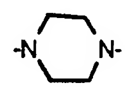
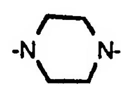
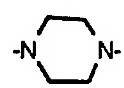
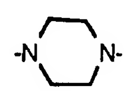
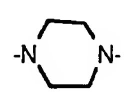
Ex.#	R[1]	R[2]	A	L	B	E	P
1433	X	Cl	$-CH_2CH_2-$ 	-NH-	H	H	COC_4H_9
1434	X	Cl	$-CH_2CH_2-$ 	-NH-	H	CH_3	$COCH_3$
1435	X	Cl	$-CH_2CH_2-$ 	-NH-	H	C_2H_5	$COCH_3$
1436	X	Cl	$-CH_2CH_2-$ 	-NH-	H	H	H
1437	X	Cl	$-CH_2CH_2-$ 	-NH-	H	CH_3	H
1438	X	Cl	$-CH_2CH_2-$ 	-NH-	H	C_2H_5	H
1439	X	Cl	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	H	$COCH_3$

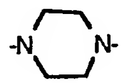
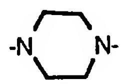
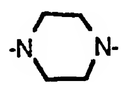
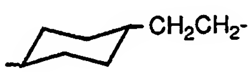
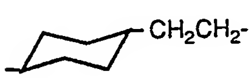
Ex.#	R^1	R^2	A	L	B	E	P
1440	X	Cl	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1441	X	Cl	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	H	COC_4H_9
1442	X	Cl	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1443	X	Cl	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1444	X	Cl	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	H	H
1445	X	Cl	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	CH_3	H
1446	X	Cl	$-CH_2CH_2-$ 	$-NHCH_2CH_2-$	H	C_2H_5	H

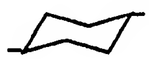
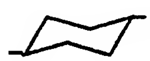
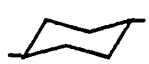
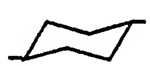
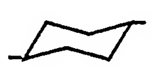
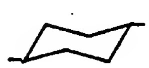
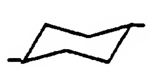
Ex.#	R1	R2	A	L	B	E	P
1447	X	Cl	$-CH_2CH_2-$ 		*	H	$COCH_3$
1448	X	Cl	$-CH_2CH_2-$ 		H	H	$COCH_2Cl$
1449	X	Cl	$-CH_2CH_2-$ 		H	H	COC_4H_9
1450	X	Cl	$-CH_2CH_2-$ 		H	CH_3	$COCH_3$
1451	X	Cl	$-CH_2CH_2-$ 		H	C_2H_5	$COCH_3$
1452	X	Cl	$-CH_2CH_2-$ 		*	H	H
1453	X	Cl	$-CH_2CH_2-$ 		H	CH_3	H

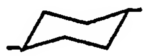
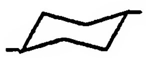
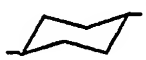
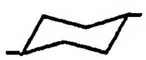
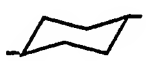
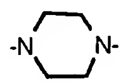
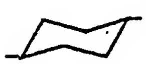
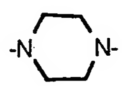
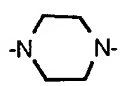
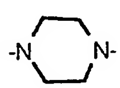
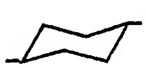
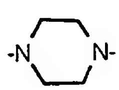
Ex.#	R1	R2	A	L	B	E	P
1454	X	Cl			H	C_2H_5	H
1455	X	Cl		-NH-	H	H	$COCH_3$
1456	X	Cl		-NH-	H	H	$COCH_2Cl$
1457	X	Cl		-NH-	H	H	COC_4H_9
1458	X	Cl		-NH-	H	CH_3	$COCH_3$
1459	X	Cl		-NH-	H	C_2H_5	$COCH_3$
1460	X	Cl		-NH-	H	H	H

Ex.#	R^1	R^2	A	L	B	E	P
1461	X	Cl		-NH-	H	CH_3	H
1462	X	Cl		-NH-	H	C_2H_5	H
1463	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_3$
1464	X	Cl		-NH-	H	H	$COCH_2Cl$
1465	X	Cl		-NH-	H	H	COC_4H_9
1466	X	Cl		-NH-	H	CH_3	$COCH_3$
1467	X	Cl		-NH-	H	C_2H_5	$COCH_3$
1468	X	Cl		$-NHCH_2CH_2-$	H	H	H

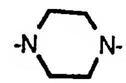
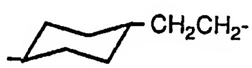
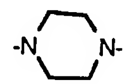
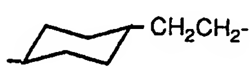
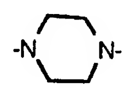
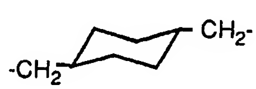
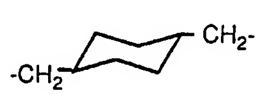
Ex.#	R^1	R^2	A	L	B	E	P
1469	X	Cl		$-NHCH_2CH_2-$	H	CH_3	H
1470	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	H
1471	X	Cl			*	H	$COCH_3$
1472	X	Cl			H	H	$COCH_2Cl$
1473	X	Cl			H	H	COC_4H_9
1474	X	Cl			H	CH_3	$COCH_3$
1475	X	Cl			H	C_2H_5	$COCH_3$

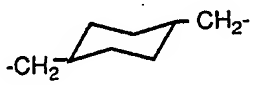
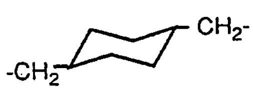
Ex.#	R1	R2	A	L	B	E	P
1476	X	Cl			*	H	H
1477	X	Cl			H	CH_3	H
1478	X	Cl			H	C_2H_5	H
1479	X	Cl		-NH-	H	H	$COCH_3$
1480	X	Cl		-NH-	H	H	$COCH_2Cl$
1481	X	Cl		-NH-	H	H	COC_4H_9

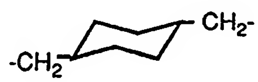
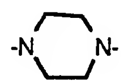
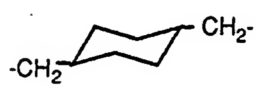
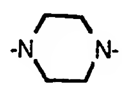
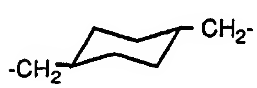
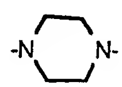
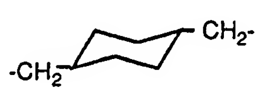
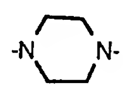
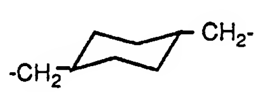
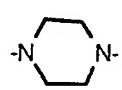
Ex. #	R^1	R^2	A	L	B	E	P
1482	X	Cl	 CH_2CH_2-	-NH-	H	CH_3	$COCH_3$
1483	X	Cl	 CH_2CH_2-	-NH-	H	C_2H_5	$COCH_3$
1484	X	Cl	 CH_2CH_2-	-NH-	H	H	H
1485	X	Cl	 CH_2CH_2-	-NH-	H	CH_3	H
1486	X	Cl	 CH_2CH_2-	-NH-	H	C_2H_5	H
1487	X	Cl	 CH_2CH_2-	$-NHCH_2CH_2-$	H	H	$COCH_3$
1488	X	Cl	 CH_2CH_2-	$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1489	X	Cl	 CH_2CH_2-	$-NHCH_2CH_2-$	H	H	COC_4H_9
1490	X	Cl	 CH_2CH_2-	$-NHCH_2CH_2-$	H	CH_3	$COCH_3$

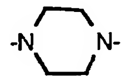
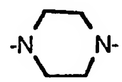
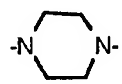
Ex.#	R^1	R^2	A	L	B	E	P
1491	X	Cl	 CH_2CH_2-	$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$
1492	X	Cl	 CH_2CH_2-	$-NHCH_2CH_2-$	H	H	H
1493	X	Cl	 CH_2CH_2-	$-NHCH_2CH_2-$	H	CH_3	H
1494	X	Cl	 CH_2CH_2-	$-NHCH_2CH_2-$	H	C_2H_5	H
1495	X	Cl	 CH_2CH_2-		*	H	$COCH_3$
1496	X	Cl	 CH_2CH_2-		H	H	$COCH_2Cl$
1497	X	Cl	 CH_2CH_2-		H	H	COC_4H_9
1498	X	Cl	 CH_2CH_2-		H	CH_3	$COCH_3$
1499	X	Cl	 CH_2CH_2-		H	C_2H_5	$COCH_3$

SUBSTITUTE SHEET

Ex.#	R^1	R^2	A	L	B	E	P
1500	X	Cl			*	H	H
1501	X	Cl			H	CH_3	H
1502	X	Cl			H	C_2H_5	H
1503	X	Cl		–NH–	H	H	$COCH_3$
1504	X	Cl		–NH–	H	H	$COCH_2Cl$
1505	X	Cl		–NH–	H	H	COC_4H_9
1506	X	Cl		–NH–	H	CH_3	$COCH_3$
1507	X	Cl		–NH–	H	C_2H_5	$COCH_3$

Ex. #	R^1	R^2	A	L	B	E	P
1508	X	Cl		-NH-	H	H	H
1509	X	Cl		-NH-	H	CH_3	H
1510	X	Cl		-NH-	H	C_2H_5	H
1511	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_3$
1512	X	Cl		$-NHCH_2CH_2-$	H	H	$COCH_2Cl$
1513	X	Cl		$-NHCH_2CH_2-$	H	H	COC_4H_9
1514	X	Cl		$-NHCH_2CH_2-$	H	CH_3	$COCH_3$
1515	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	$COCH_3$

Ex.#	R1	R2	A	L	B	E	P
1516	X	Cl		$-NHCH_2CH_2-$	H	H	H
1517	X	Cl		$-NHCH_2CH_2-$	H	CH_3	H
1518	X	Cl		$-NHCH_2CH_2-$	H	C_2H_5	H
1519	X	Cl			*	H	$COCH_3$
1520	X	Cl			H	H	$COCH_2Cl$
1521	X	Cl			H	H	COC_4H_9
1522	X	Cl			H	CH_3	$COCH_3$
1523	X	Cl			H	C_2H_5	$COCH_3$

Ex.#	R^1	R^2	A	L	B	E	P
1524	X	Cl			*	H	H
1525	X	Cl			H	CH_3	H
1526	X	Cl			H	C_2H_5	H

BIOLOGICAL EVALUATION

Compounds of Examples 1-80 are suitable angiotension II antagonists for use as the first component of conjugates of the invention. The AII receptor binding activity of many of the Example #1-#80 compounds, for example, is described in EP #253,310 published 20 January 1988. The compound of Example #5 was further evaluated in three biological assays (Assays "A", "B" and "C") for AII antagonist and blood pressure lowering properties. In two other assays, blood-pressure lowering effects of the conjugate of Example #81 were evaluated (Assays "D" and "E").

Assay A: Angiotensin II Binding Activity

Compound of Example #5 was tested for ability to bind to the smooth muscle angiotensin II receptor using a rat uterine membrane preparation. Angiotensin II (AII) was purchased from Peninsula Labs. ^{125}I-angiotensin II (specific activity of 2200 Ci/mmol) was purchased from Du Pont-New England Nuclear. Other chemicals were obtained from Sigma Chemical Co. This assay was carried out according to the method of Douglas et al [Endocrinology, 106, 120-124 (1980)]. Rat uterine membranes were prepared from fresh tissue. All procedures were carried out at 4°C. Uteri were stripped of fat and homogenized in phosphate-buffered saline at pH 7.4 containing 5 mM EDTA. The homogenate was centrifuged at 1500 x g for 20 min., and the supernatant was recentrifuged at 100,000 x g for 60 min. The pellet was resuspended in buffer consisting of 2 mM EDTA and 50 mM Tris-HCl (pH 7.5) to a final protein concentration of 4 mg/ml. Assay tubes were charged with 0.25 ml of a solution containing 5 mM $MgCl_2$, 2 mM EDTA, 0.5% bovine serum albumin, 50 mM Tris-HCl, pH 7.5 and ^{125}I-AII (approximately 10^5 cpm) in the absence or in the presence of unlabelled ligand. The reaction was initiated by the addition of membrane protein and the mixture was

incubated at 25°C for 60 min. The incubation was terminated with ice-cold 50 mM Tris-HCl (pH 7.5) and the mixture was filtered to separate membrane-bound labelled peptide from the free ligand. The incubation tube and filter were washed with ice-cold buffer. Filters were assayed for radioactivity in a Micromedic gamma counter. Nonspecific binding was defined as binding in the presence of 10 µM of unlabelled AII. Specific binding was calculated as total binding minus nonspecific binding. The receptor binding affinity of an AII antagonist compound was indicated by the concentration (IC_{50}) of the tested AII antagonist which gives 50% displacement of the total specifically bound ^{125}I-AII from the high affinity AII receptor. Binding data were analyzed by a nonlinear least-squares curve fitting program. Results are reported in Table VIII.

Assay B: In Vitro Vascular Smooth Muscle-Response for AII

Compound of Example #5 was tested for AII antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2-2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue and then cut into 3-mm ring segments. The endothelium was removed from the rings by gently sliding a rolled-up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37°C, between moveable and fixed ends of a stainless steel wire with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled with 20 ml of oxygenated (95% oxygen/5% carbon dioxide) Krebs solution of the following composition (nM): 130 NaCl, 15 $NaHCO_3$, 15 KCl, 1.2 NaH_2PO_4, 1.2 $MgSO_4$, 2.5 $CaCl_2$, and 11.4 glucose. The preparations were equilibrated for one hour before approximately one gram of passive tension was placed on the rings. Angiotensin II concentration-response curves were then recorded (3 X 10^{-10}

to 1 X 10^{-5} M). Each concentration of AII was allowed to elicit its maximal contraction, and then AII was washed out repeatedly for 30 minutes before rechallenging with a higher concentration of AII. Aorta rings were exposed to the test antagonist at 10^{-5} M for 5 minutes before challenging with AII. Adjacent segments of the same aorta ring were used for all concentration-response curves in the presence or absence of the test antagonist. The effectiveness of the test compound was expressed in terms of pA_2 values and were calculated according to H.O. Schild [Br. J. Pharmacol. Chemother., 2,189-206 (1947)]. The pA_2 value is the concentration of the test antagonist compound which increases the EC_{50} value for AII by a factor of two. The test compound was evaluated in aorta rings from three rabbits. Results are reported in Table VIII.

TABLE VIII

In Vitro Angiotensin II Activity of Compounds of Formula I

Test Compound	[1]Assay A IC_{50} (nM)	[2]Assay B PA_2
Ex. #5	216 ± 45	7.13 ± 0.16

[1]Assay A: In Vitro angiotensin II Binding Activity
[2]Assay B: In Vitro Vascular Smooth Muscle Response

Assay C: In Vivo Intraduodenal and Intravenous Pressor Assay Response for AII Antagonists

The in vivo AII receptor antagonist activity of Example #5 compound was examined in ganglion-blocked male Sprague-Dawley rats (Harlan Sprague-Dawley, Inc.), weighing 300-400 g, anesthetized with 100 mg/kg i.p. Inactin. Catheters (PE-50) were implanted in a femoral artery and vein to measure mean arterial pressure and to administer compounds, respectively. A tracheal catheter maintained airway patency. For intravenous experiments, autonomic neurotransmission was blocked by teatment with mecamylamine (3 mg/kg i.v.) and atropine (400 µg/kg i.v.). AII (30 ng/kg i.v., 20-25 µl volume) was administered four times at 10 minute intervals to establish a reproducible control pressor response. Example #5 compound was then administered at 1, 3 and 10 mg/kg in separate groups of rats as an intravenous bolus (0.2 ml volume) before rechallenging with AII

(30 ng/kg, 20-25 µl volume) for the following 2 hours. For intraduodenal experiments, rats were anesthetized as above, but ganglion blockade was not performed. AII was administered at 100 ng/kg i.v. (20-25 µl volume), and was administered at 10, 30 and 100 mg/kg in separate groups of rats as an intraduodenal bolus (0.2 ml volume). Angiotensin II injections were then given 5, 10, 20, 30, 45, 60, 75, 90, and 120 minutes after administration of the test compound and response of arterial pressure was monitored. The response to AII was calculated as percent of the control response and then the percent inhibition was calculated as 100 minus the percent control response. Duration of action of a test compound was defined as the time from peak percent inhibition to 50% of peak. The test compound was tested in two rats and the values for the two rats were averaged. Results are reported in Tables IX and X as percent of the control of AII pressor response, where "control" is defined as AII pressor response before the AII antagonist test compound is administered.

TABLE IX

In Vivo Intravenous Angiotensin II
Activity of Example #5 Compound
(% Control of AII Pressor Response)

Dose (mg/kg)	Time (min)										
	1	5	10	20	30	40	50	60	75	90	120
1 n=4	80 ±3	85 ±4	92 ±4	90 ±6	88 ±5	86 ±5	86 ±6	89 ±5	93 ±3	95 ±5	100 ±0
3 n=4	39 ±5	55 ±7	63 ±8	68 ±6	74 ±7	75 ±5	75 ±3	81 ±7	88 ±7	92 ±5	98 ±1
10 n=6	4 ±2	16 ±2	23 ±2	31 ±2	40 ±3	47 ±4	51 ±4	60 ±6	71 ±7	80 ±8	96 ±6

TABLE X

In Vivo Intraduodenal Angiotensin II Activity
of Example #5 Compound
(% Control of AII Pressor Response)

Dose mg/kg	Time (min)								
	1	5	10	20	30	40	50	60	75
10 n=3	100 ±0	94 ±4	99 ±1	85 ±11	91 ±9	91 ±9	95 ±5	93 ±7	95 ±5
30 n=4	48 ±4	48 ±7	44 ±11	28 ±5	34 ±4	42 ±6	41 ±0	53 ±2	74 ±7
100 n=4	28 ±3	19 ±4	15 ±3	14 ±8	9 ±5	5 ±2	13 ±6	10 ±4	13 ±5

Assay D: *In Vivo* Effects of Chronic Infusion of Conjugate of the Invention

A conjugate of the invention as synthesized in Example 81 was evaluated biologically by an in vivo assay to determine the ability of the conjugate to selectively inhibit renal action and thereby control blood pressure. This in vivo experiment was conducted to characterize the effects of the Example 81 conjugate on spontaneously hypertensive rats (SHR) by acute administration i.v. and by chronic administration i.v. The Example 81 compound or saline vehicle was infused continuously for four days in SHR. Mean arterial pressure was measured (Gould Chart Recorder, model 3800; Statham P23Db pressure transducer) via an indwelling femoral artery catheter between 10:00 A. M. and 2:00 P. M. each day. The Example 81 conjugate (10 mg/hr) or saline was infused via a jugular vein catheter with a Harvard infusion pump. After administration of the Example 81 conjugate, there was observed a lowered mean arterial pressure as compared to the saline vehicle control as reported in Table XI and also in Fig. 1. A test was conducted to determine whether the Example 81 conjugate would antagonize non-renal, vascular angiotensin II receptors. In this test AII was administered by bolus injection (100 ng/kg) to the SHR rats (described above) on the control day and on days 1, 2 and 3 during conjugate infusion. No evidence for systemic angiotensin II receptor antagonism was observed, given the similar pressor responses to injections of angiotensin II on the control day and days 1, 2 and 3 of infusion of the Example 81 conjugate as shown in Table XII and also in Figure 2.

TABLE XI

Effect of Ex. #81 Conjugate on Mean Arterial Pressure: Chronic Administration

Time (days):	Control	1	2	3
MAP (mm Hg)	163	148	135	140

TABLE XII

Effect of Ex. #81 Conjugate on AII Pressor Response

Time (days):	Control	1	2	3
MAP (mm Hg)	44	45	65	60

Assay "E": *In Vivo* Effects of Acute Infusion of Conjugate of the Invention

In this assay, a comparison was made between an angiotensin II antagonist compound (Ex. #5) and a glutamyl conjugate (Ex. #81) of the Ex. #5 AII antagonist compound to determine the renal selectivity of the conjugate. Male Sprague-Dawley rats (300-350 g body weight) had catheters implanted into the femoral artery and vein under chloral hydrate anesthesia (400 mg/kg, i.p.). After 2 to 4 days of recovery, on the experimental day, a urinary bladder catheter was implanted under methohexital anesthesia (50 mg/kg, i.p.). Rats were placed in a restraint device to allow for urine collection and mean arterial pressure measurements. After 1-2 hours of recovery, in conscious rats, an isotonic saline infusion (50 µl/min) was started and continued for the duration of the experiment. After one hour equilibration to the saline infusion, a 20 minute control urine and mean arterial pressure collection were obtained. Then angiotensin II was infused at 20 ng/min for 25 minutes. After 5 minutes of angiotensin II infusion, a 20 minute experimental collection was made. Finally, 5 minutes after the end of angiotensin II infusion, a 20 minute recovery collection was obtained. In separate groups of rats, vehicle (0.3 ml isotonic saline, i.v. bolus), Example #5 angiotensin II antagonist compound (100 mg/kg, i.v. bolus), or Example #81 conjugate (100 mg/kg, i.v. bolus) was administered 1-2 minutes prior to onset of angiotensin II infusion. Infusion of angiotensin II increased mean arterial pressure and decreased urinary sodium excretion. The Example #5 AII antagonist compound prevented both responses to angiotensin II. The Example #81 conjugate had no effect on the mean arterial pressure response but prevented the antinatriuretic response to angiotensin II. Angiotensin II infusion following administration of Example #81 conjugate actually increased urinary sodium excretion, probably due to a pressure natriuresis. Results are shown in Tables

XIII and XIV and also in Figs. 3 and 4. Data are presented as means ± SE. Repeated measures analysis of variance was used for main effects and interactions and Tukey's HSD test was used for pairwise comparisons among means. Statistical significance was defined as $p<0.05$.

TABLE XIII

Effect of Ex. #81 Conjugate on Urinary Sodium Excretion (µEq/min/100 g BW)

	Control	AII	Recovery
Vehicle	1.9 ± 0.8	0.8 ± 0.3*	1.7 ± 0.5
Ex. #5	2.4 ± 0.5	2.5 ± 1.1	2.6 ± 0.7
Ex. #81	1.3 ± 0.3	4.1 ± 1.3*	1.8 ± 0.4

TABLE XIV

Effect of Ex. #81 Conjugate on Mean Arterial Pressure (mm Hg): Acute Administration

	Control	AII	Recovery
Vehicle (n=6)	121 ± 3	155 ± 3*	123 ± 4
Ex. #5 (n=6)	123 ± 5	125 ± 7	124 ± 7
Ex. #81 (n=6)	117 ± 3	151 ± 4*	121 ± 4

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more conjugates which comprises a first component selected from angiotensin II antagonist compounds of Formula I linked to a second component provided by an enzyme-cleavable moiety. Such pharmaceutical compositions further comprise one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The conjugates of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of a conjugate of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The conjugates and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the conjugate. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of conjugate from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.

The conjugate may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred daily dose would be from about 1 to 30 mg/kg body weight. Conjugates indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 100 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 100 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 50 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

The dosage regimen for treating a disease condition with the conjugates and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular conjugate employed, and thus may vary widely.

For therapeutic purposes, the conjugates of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered <u>per os</u>, the conjugate may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium

and calcium salts of phosphoric and sulfur... acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of conjugate in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The conjugates may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

WHAT IS CLAIMED IS:

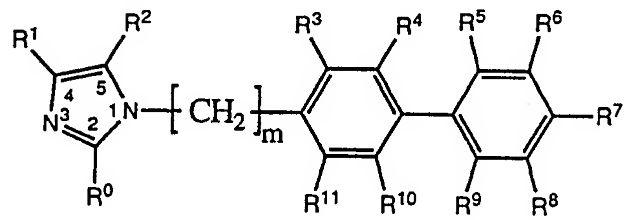
1. A conjugate comprising a residue of an angiotensin II antagonist compound, said conjugate being renal selective.

2. Conjugate of Claim 1 comprising a first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is provided by an angiotensin II antagonist compound, and wherein said second residue is capable of being cleaved from said first residue selectivity in the kidney.

3. Conjugate of Claim 2 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

4. Conjugate of Claim 3 wherein said angiotensin II antagonist compound providing said first residue is selected from biphenylmethyl 1H-substituted-1,3-imidazole compounds.

5. Conjugate of Claim 4 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:

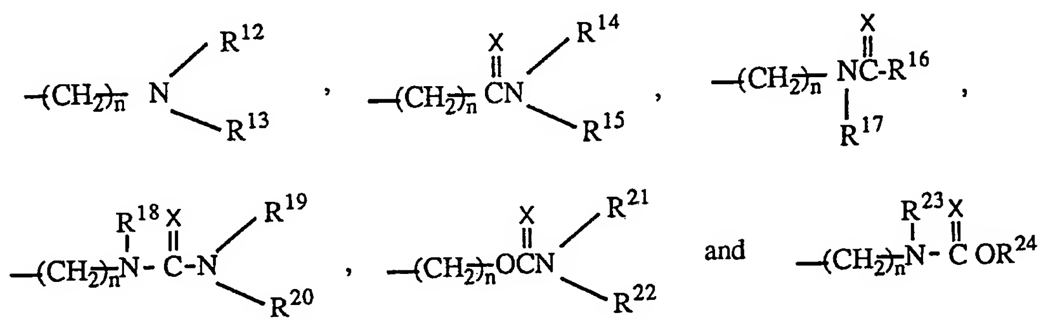


(I)

wherein m is a number selected from one to four, inclusive;

wherein each of R^0 through R^{11} is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl,

arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing groups has one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{16} and R^{17} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form an aromatic heterocyclic

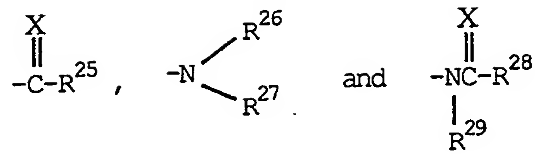
group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

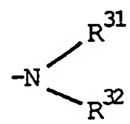
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

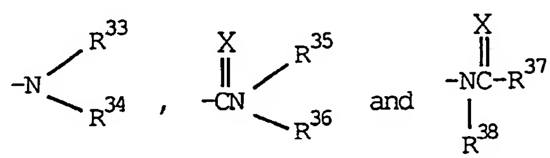
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR^{30} and



wherein D is selected from oxygen atom and sulfur atom and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each of R^{33}, R^{34}, R^{35}, R^{36}, R^{37} and R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R^{26} and R^{27} taken together and R^{28} and R^{29} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical,

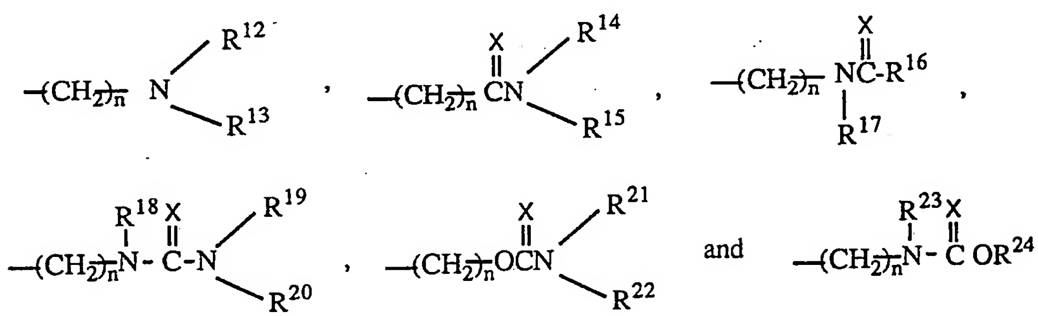
which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{26} and R^{27} taken together and R^{31} and R^{32} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

6. Conjugate of Claim 5 wherein m is one; wherein each of R^0 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio,

aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

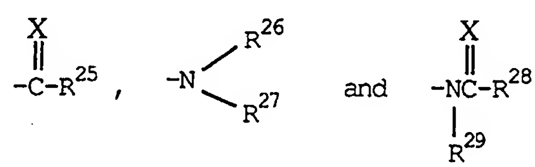
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

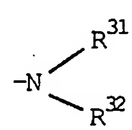
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula

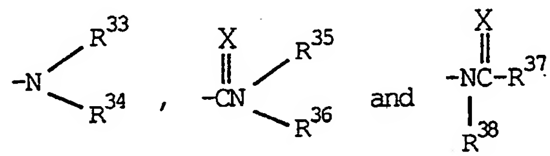


wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl,

cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

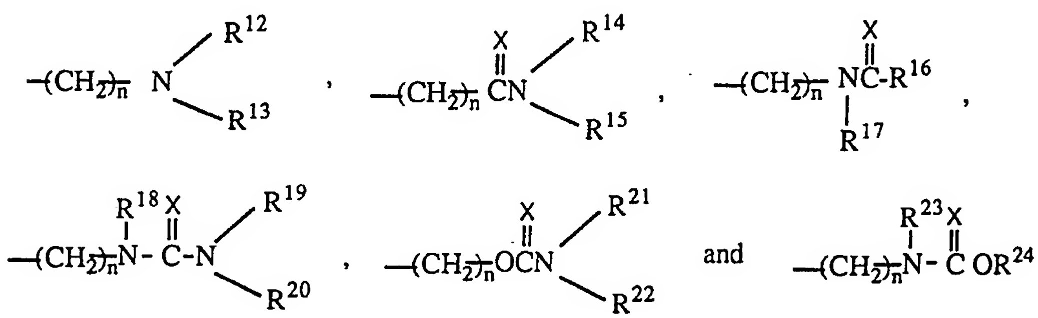
wherein each of R^{26} through R^{31} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

7. Conjugate of Claim 6 wherein m is one; wherein each of R^0 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl,

alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalklylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen taom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

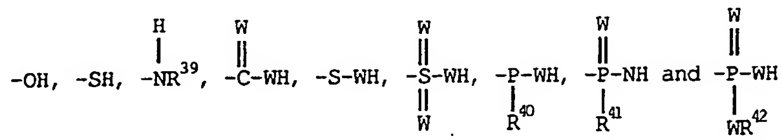
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

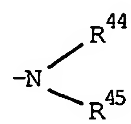
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{40}, R^{41}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39}, R^{40}, R^{41} and R^{42} may be further independently selected from amino radicals of the formula

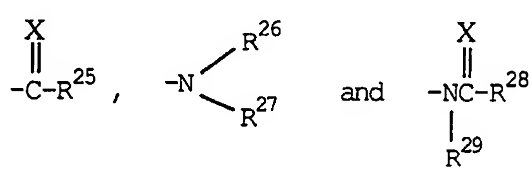


wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R^{40} and R^{41} may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

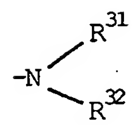
wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, wherein R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

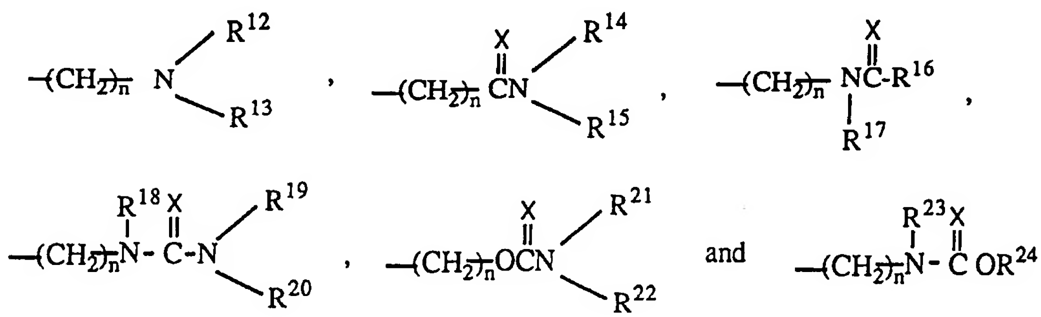
wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

8. Conjugate of Claim 7 wherein m is one; wherein each of R^0, R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl

and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

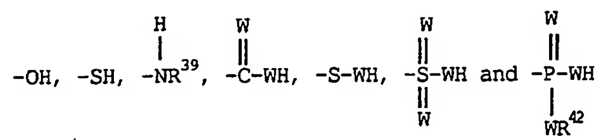
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

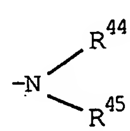
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen

and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

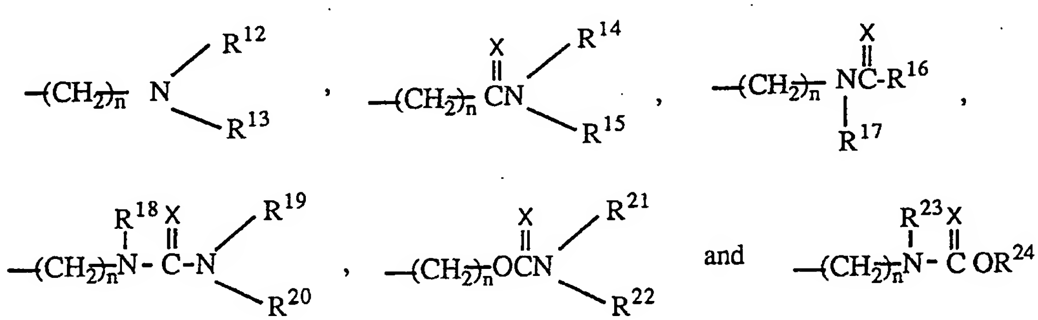
wherein each of R^1 through R^{24}, Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

9. Conjugate of Claim 8 wherein m is one; wherein each of R^0, R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl,

cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

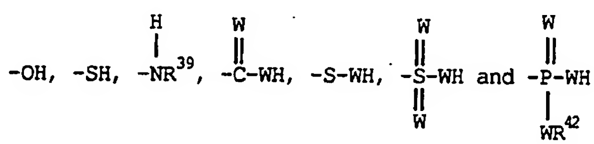
wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl,

phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

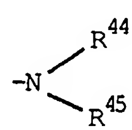
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from

oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

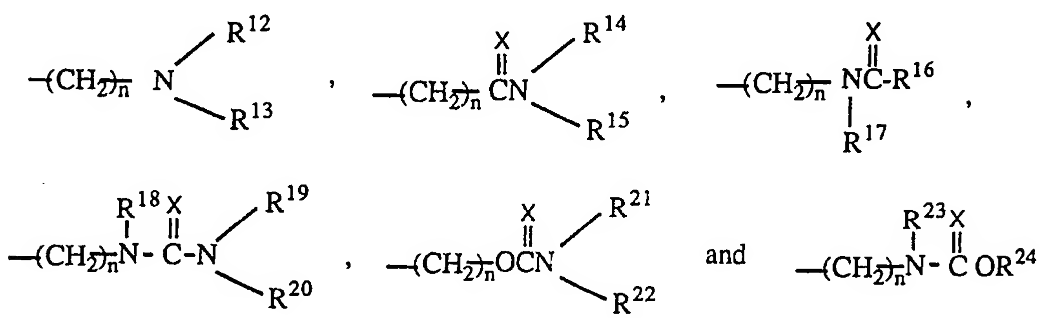
wherein each of R^1 through R^{24}, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

10. Conjugate of Claim 9 wherein m is one; wherein R^0 is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of R^1 and R^2 is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl,

alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



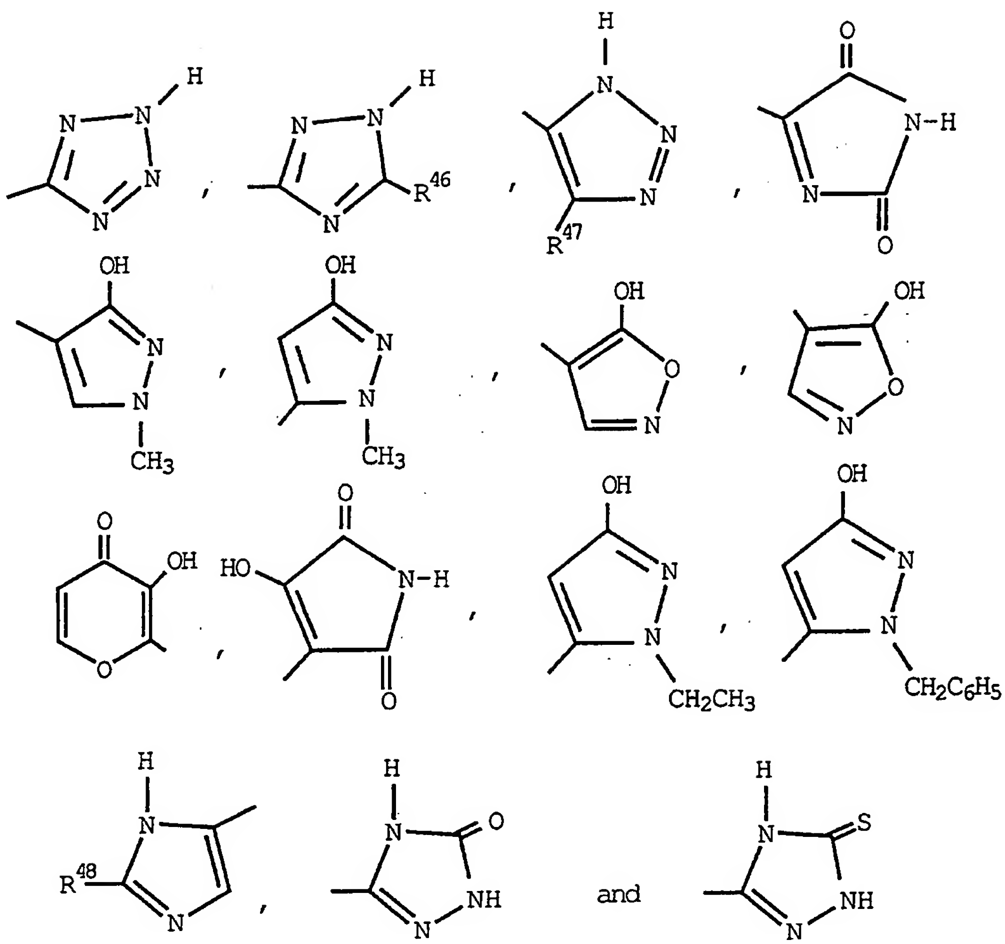
wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

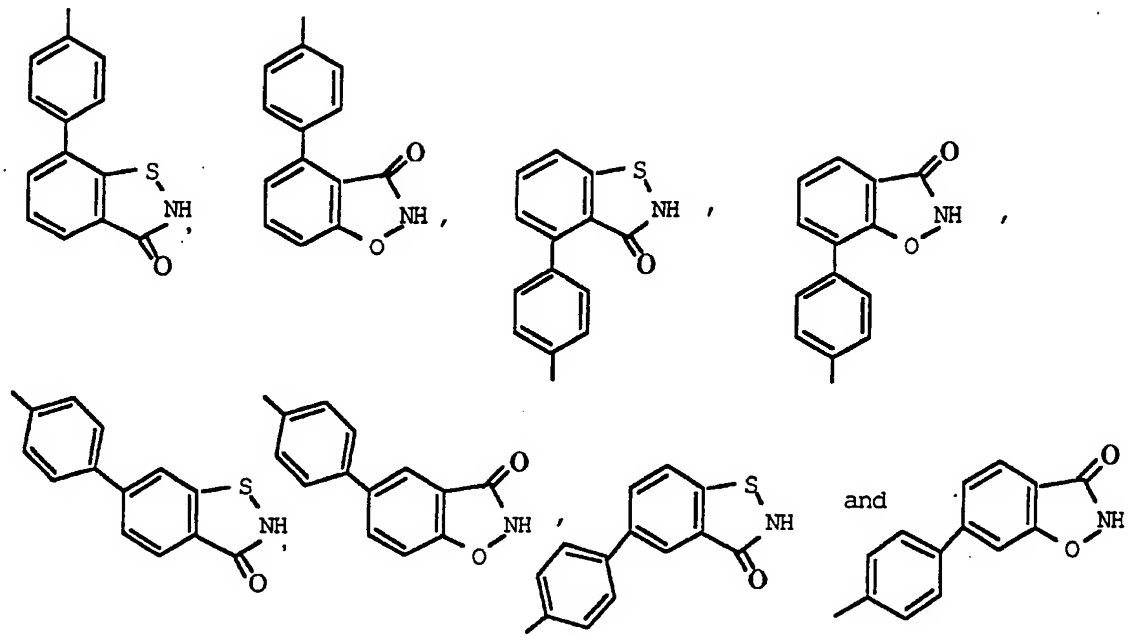
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties consisting of CO_2H, CO_2CH_3, SH, CH_2SH, C_2H_4SH, PO_3H_2, $NHSO_2CF_3$, $NHSO_2C_6F_5$, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, $CONHOCH_3$, $CONHOC_2H_5$, $CONHCF_3$, OH, CH_2OH, C_2H_4OH, OPO_3H_2, OSO_3H ,



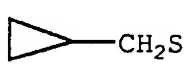
wherein each of R^{46}, R^{47} and R^{48} is independently selected from H, Cl, CN, NO_2, CF_3, C_2F_5, C_3F_7, CHF_2, CH_2F, CO_2CH_3, $CO_2C_2H_5$, SO_2CH_3, SO_2CF_3 and $SO_2C_6F_5$; wherein Z is selected from O, S, NR^{49} and CH_2; wherein R^{49} is selected from hydrido, CH_3 and $CH_2C_6H_5$; and wherein said acidic moiety may be a heterocyclic acidic group attached at any two adjacent positions of R^3 through R^{11} so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from

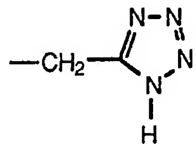


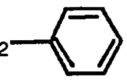
and the esters, amides and salts of said acidic moieties;

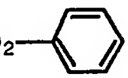
with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

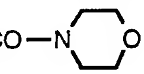
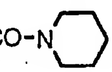
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

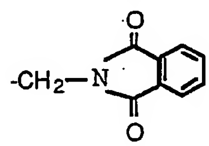
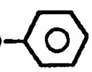
11. Conjugate of Claim 10 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH{=}CH$, $C_3H_7(N)$, SC_3H_7, , , C_2H_5, $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9,  , $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH$-; wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO,

CH_2CO_2H, $CH(CH_3)CO_2H$, NO_2, Cl, ,

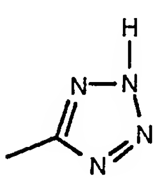
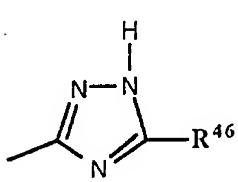
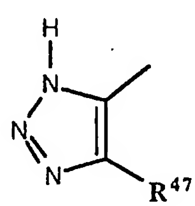
$-CH_2OCOCH_2CH_2-$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,

$-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H,

$-CH_2CH_2-CO-$, $-CH_2CH_2CO-$, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2OCSNHCH_3$, $-CH_2NHCSOC_3H_7$,

$-CH_2CH_2CH_2F$, $-CH_2ONO_2$, , $-CH_2SH$, $-CH_2O-$,

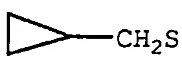
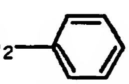
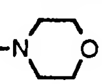
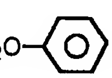
12. Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

,  and 

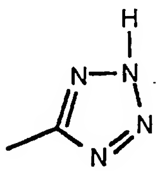
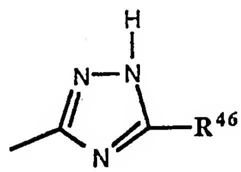
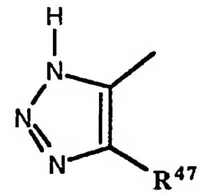
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

12. Conjugate of Claim 11 wherein m is one; wherein R^0 is sel :cted from $C_4H_9(n)$, $CH_3CH_2CH{=}CH$, $C_3H_7(N)$, SC_3H_7, , , C_2H_5, $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9, , $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH-$; wherein R^1 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO, CH_2CO_2H, $CH(CH_3)CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$, $-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H, $-CH_2CH_2-CO-$, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2CH_2CH_2F$, $-CH_2SH$ and $-CH_2O-$; wherein R^2 is selected from H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-.xopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group

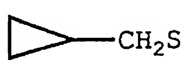
selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

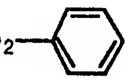
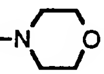
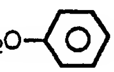
 ,  and 

wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

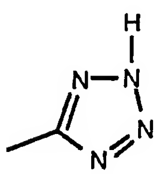
with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

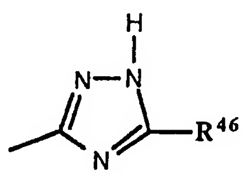
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

13. Conjugate of Claim 11 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH{=}CH$, $C_3H_7(N)$, SC_3H_7, , , C_2H_5, $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9,  , $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH-$; wherein R^1 is selected from H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO, CH_2CO_2H, $CH(CH_3)CO_2H$, , $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,

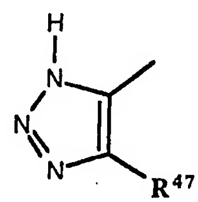
$-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H, $-CH_2CH_2-CO-$, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2CH_2CH_2F$, $-CH_2SH$ and $-CH_2O-$;

wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,





and



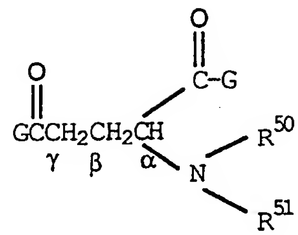
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

14. Conjugate of Claim 3 wherein said second residue forms a kidney-enzyme-cleavable amide bond with the residue of said angiotensin II antagonist compound.

15. Conjugate of Claim 14 wherein said second residue is provided by a compound of Formula II:



(II)

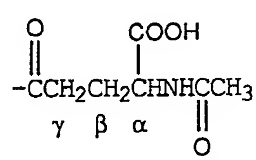
wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{52}$, $-SR^{53}$ and $>NR^{54}$ with each of R^{52}, R^{53} and R^{54} independently selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

16. Conjugate of Claim 15 wherein each G substituent is hydroxy.

17. Conjugate of Claim 16 wherein each G substituent is hydroxy; wherein R^{50} is hydrido; and wherein R^{51} is selected from

$-\overset{\overset{\displaystyle O}{\|}}{C}R^{55}$ wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

18. Conjugate of Claim 17 wherein said second residue is



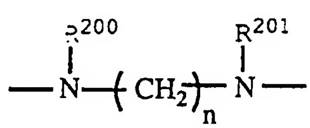
19. Conjugate of Claim 18 wherein said first residue is an angiotensin II antagonist compound containing

a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

20. Conjugate of Claim 3 wherein said first residue is an angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

21. Conjugate of Claim 20 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

22. Conjugate of Claim 21 wherein said diamino-terminated linker group is a divalent radical of Formula III:

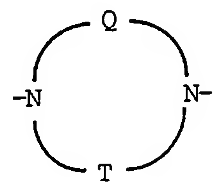


(III)

wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

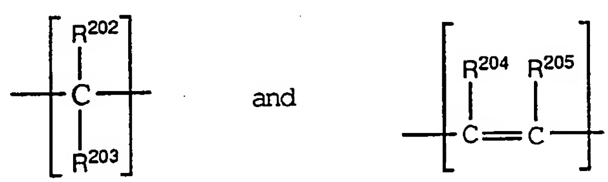
23. Conjugate of Claim 24 wherein each of R^{200} and R^{201} is hydrido.

24. Conjugate of Claim 21 wherein said diamino-terminated linker group is a divalent radical of Formula IV:



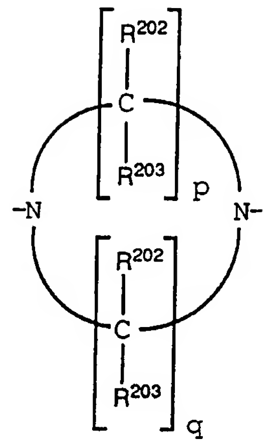
(IV)

wherein each of Q and T is one or more groups independently selected from



wherein each of R^{202} through R^{205} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

25. Conjugate of Claim 24 wherein said diamino-terminated linker group is a divalent radical of Formula V:



(V)

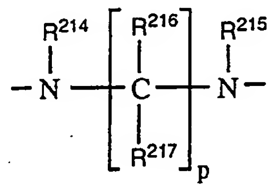
wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

26. Conjugate of Claim 25 wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

27. Conjugate of Claim 26 wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

28. Conjugate of Claim 27 wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two.

29. Conjugate of Claim 21 wherein said diamino-terminated linker group is a divalent radical of Formula VI:



(VI)

wherein each of R^{214} through R^{217} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

30. Conjugate of Claim 29 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.

31. Conjugate of Claim 30 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido and alkyl; and wherein p is two.

32. Conjugate of Claim 31 wherein each of R^{214}, R^{215}, R^{216} and R^{217} is hydrido; and wherein p is two.

33. Conjugate of Claim 12 wherein said angiotensin II antagonist compound is 4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

34. Conjugate of Claim 33 which is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-

1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

35. Conjugate of Claim 33 which is N^2-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine.

36. Conjugate of Claim 33 which is N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide.

37. Conjugate of Claim 13 wherein said angiotensin II antagonist compound is 4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

38. Conjugate of Claim 37 which is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

39. Conjugate of Claim 37 which is N^2-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine.

40. Conjugate of Claim 37 which is N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide.

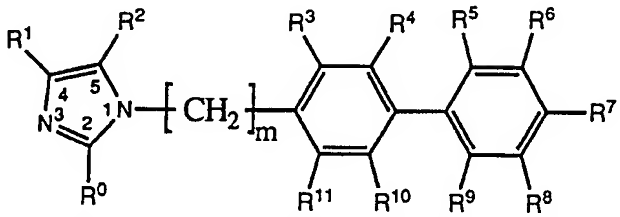
41. A pharmaceutical composition comprising one or more pharmaceutically-acceptable carriers or diluents and a therapeutically-effective amount of a renal-selective conjugate, said conjugate comprising a residue of an angiotensin II antagonist compound.

42. The composition of Claim 41 wherein said conjugate comprises first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is provided by an angiotensin II antagonist compound, and wherein said second residue is capable of being cleaved from said first residue.

43. The composition of Claim 42 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

44. The composition of Claim 43 wherein said angiotensin II antagonist compound providing said first residue is selected from biphenylmethyl 1H-substituted-1,3-imidazole compounds.

45. The composition of Claim 44 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:

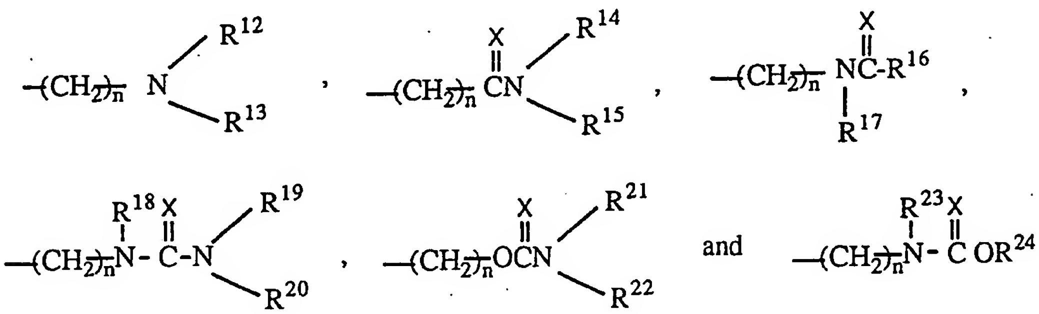


(I)

wherein m is a number selected from one to four, inclusive;

wherein each of R^0 through R^{11} is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbony: :io, a'kylthiocarbonyl, aralkylthiocarbony. .io, m.rcapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing groups has one or more ring atoms selected from oxygen,

sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

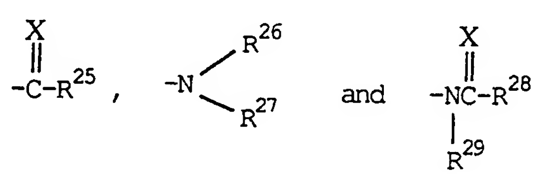
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{16} and R^{17} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

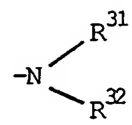
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

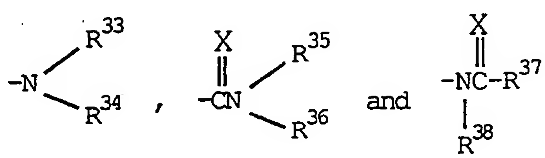
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR^{30} and



wherein D is selected from oxygen atom and sulfur atom and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each of R^{33}, R^{34}, R^{35}, R^{36}, R^{37} and R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R^{26} and R^{27} taken together and R^{28} and R^{29} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{26} and R^{27} taken together and R^{31} and R^{32} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical

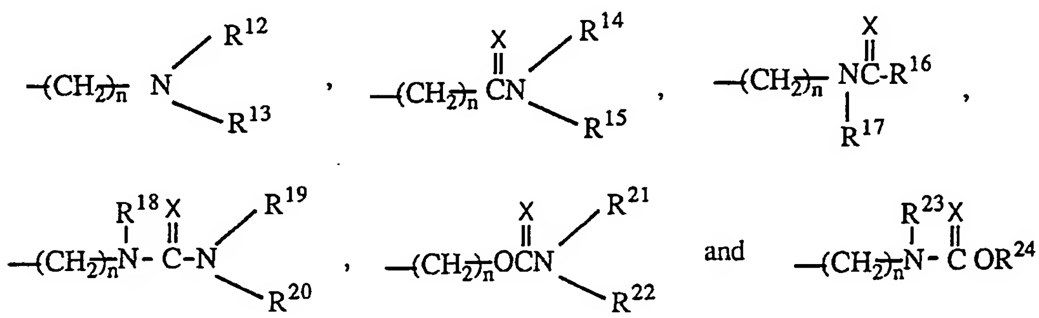
and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

46. The composition of Claim 45 wherein m is one; wherein each of R^0 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthio-carbonylthio, alkylthiothiocarbonyl, alkylthiothio-carbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has

one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

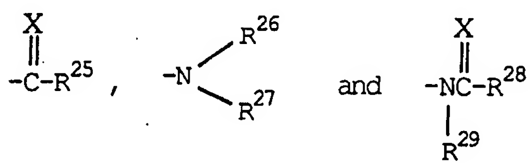
and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

$$-Y_nA$$

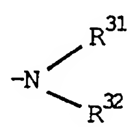
wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl,

cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

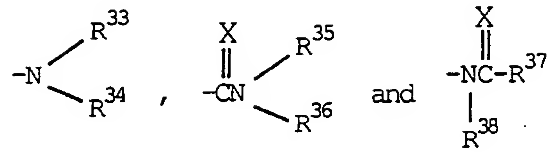
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

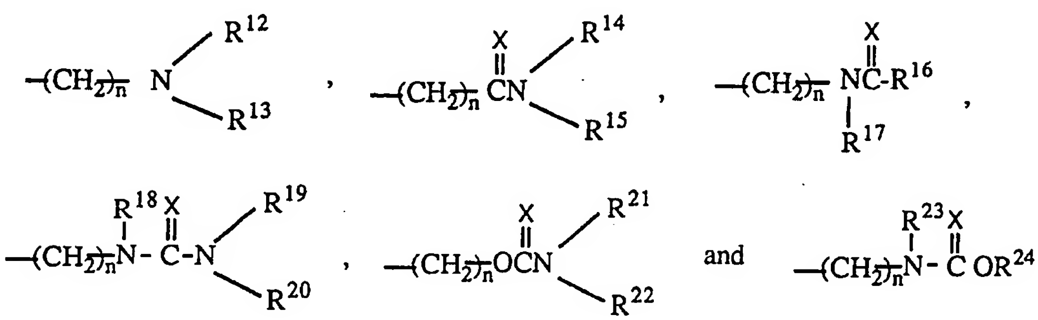
wherein each of R^{26} through R^{31} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

47. The composition of Claim 46 wherein m is one; wherein each of R^0 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalklylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one

or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen taom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

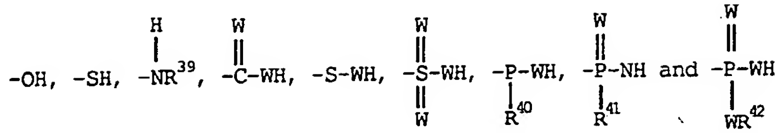
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

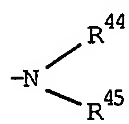
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{40}, R^{41}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39}, R^{40}, R^{41} and R^{42} may be further independently selected from amino radicals of the formula



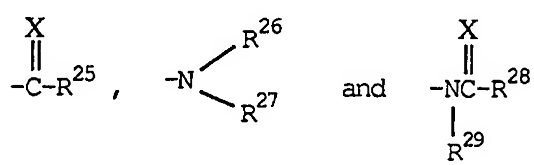
wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R^{40} and R^{41} may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of

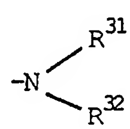
heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, wherein R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

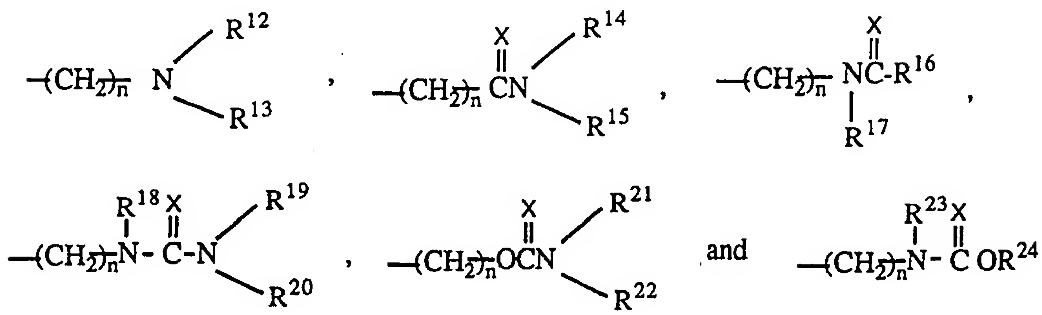
wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

48. The composition of Claim 47 wherein m is one; wherein each of R^0, R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be

further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

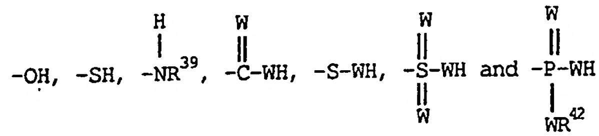
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

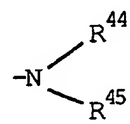
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one

hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

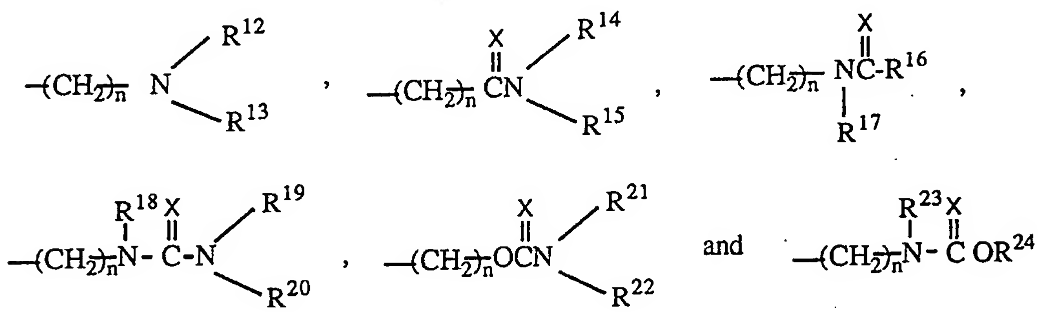
wherein each of R^1 through R^{24}, Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

49. The composition of Claim 48 wherein m is one; wherein each of R^0, R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy,

alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

$$-OH,\ -SH,\ -\overset{\displaystyle H}{\overset{|}{N}}R^{39},\ -\overset{\displaystyle W}{\overset{\|}{C}}-WH,\ -S-WH,\ -\underset{\displaystyle W}{\underset{\|}{\overset{\displaystyle W}{\overset{\|}{S}}}}-WH \text{ and } -\underset{\displaystyle WR^{42}}{\underset{|}{\overset{\displaystyle W}{\overset{\|}{P}}}}-WH$$

wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula

$$-N\begin{matrix} \diagup R^{44} \\ \diagdown R^{45} \end{matrix}$$

wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3

through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

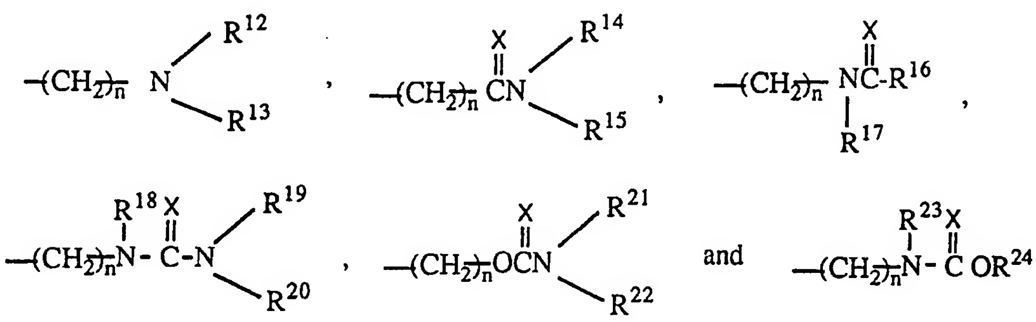
wherein each of R^1 through R^{24}, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

50. The composition of Claim 49 wherein m is one; wherein R^0 is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of R^1 and R^2 is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl,

phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



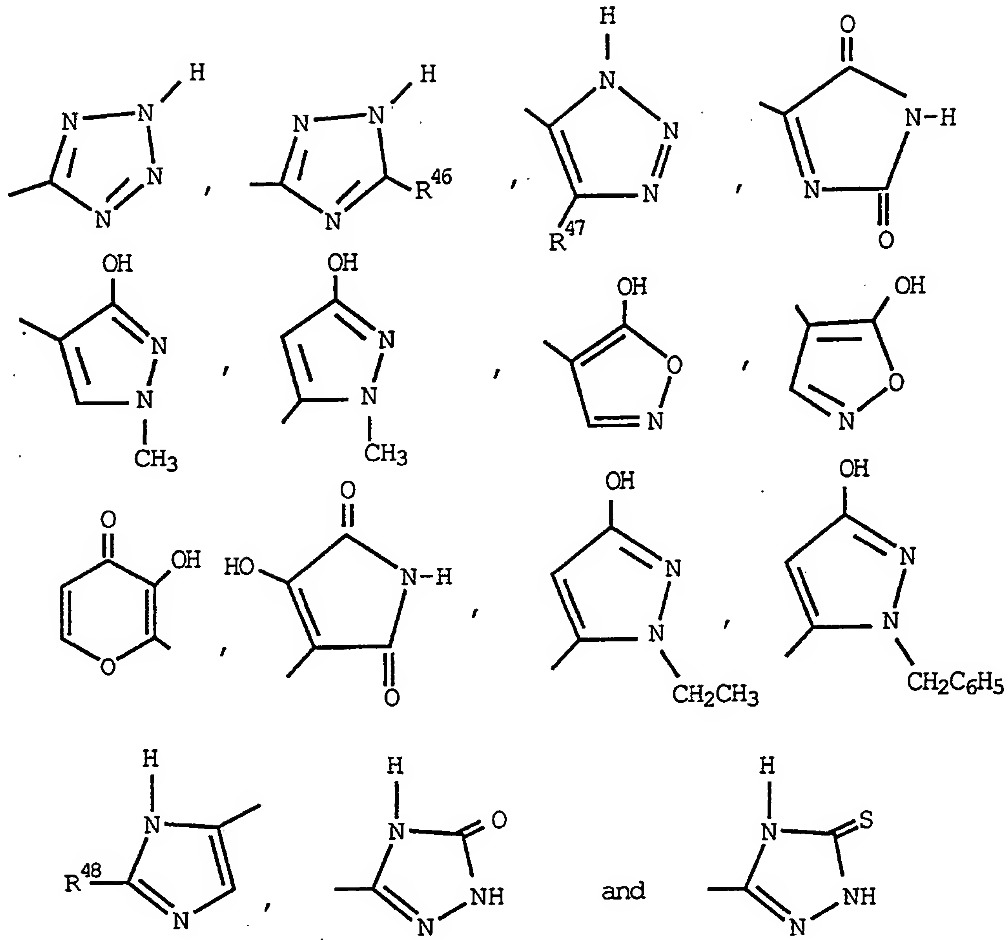
wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

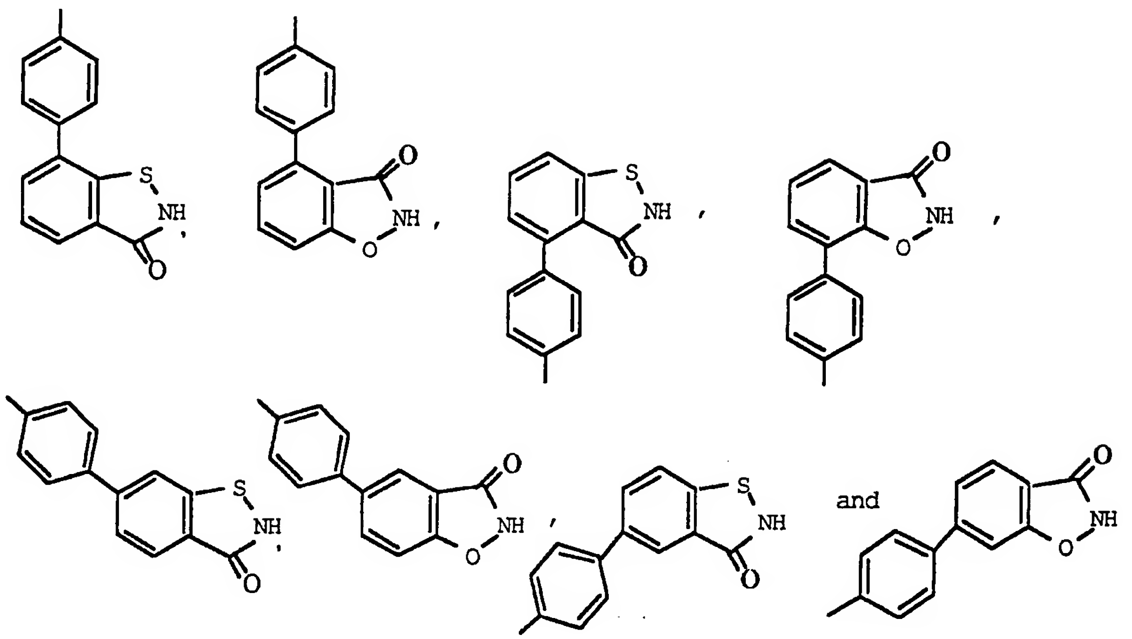
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties consisting of CO_2H, CO_2CH_3, SH, CH_2SH, C_2H_4SH, PO_3H_2, $NHSO_2CF_3$, $NHSO_2C_6F_5$, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, $CONHOCH_3$, $CONHOC_2H_5$, $CONHCF_3$, OH, CH_2OH, C_2H_4OH, OPO_3H_2, OSO_3H ,



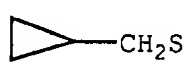
wherein each of R^{46}, R^{47} and R^{48} is independently selected from H, Cl, CN, NO_2, CF_3, C_2F_5, C_3F_7, CHF_2, CH_2F, CO_2CH_3, $CO_2C_2H_5$, SO_2CH_3, SO_2CF_3 and $SO_2C_6F_5$; wherein Z is selected from O, S, NR^{49} and CH_2; wherein R^{49} is selected from hydrido, CH_3 and $CH_2C_6H_5$; and wherein said acidic moiety may be a heterocyclic acidic group attached at any two adjacent positions of R^3 through R^{11} so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from

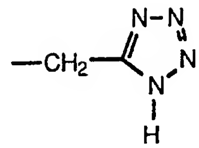


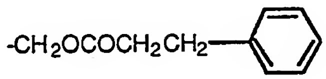
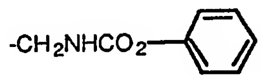
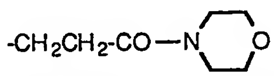
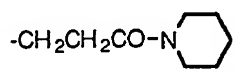
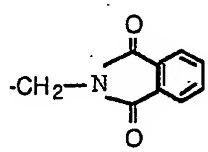
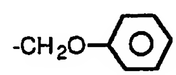
and the esters, amides and salts of said acidic moieties;

with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

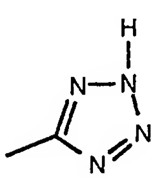
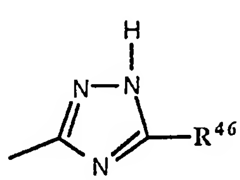
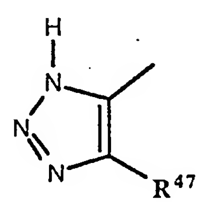
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

51. The composition of Claim 50 wherein m is one; wherein R^0 is selected from C_4H_9(n), $CH_3CH_2CH{=}CH$, C_3H_7(N), SC_3H_7, , , C_2H_5, C_5H_{11}(n), C_6H_{13}(n), SC_4H_9, , $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH$-; wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO,

CH_2CO_2H, $CH(CH_3)CO_2H$, NO_2, Cl,  ,

, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$, $-CH_2-NHCO_2C_2H_5$, , $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H, , , $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2OCSNHCH_3$, $-CH_2NHCSOC_3H_7$, $-CH_2CH_2CH_2F$, $-CH_2ONO_2$, , $-CH_2SH$, ,

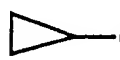
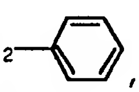
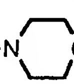
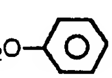
52. Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

 ,  and 

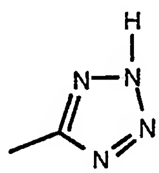
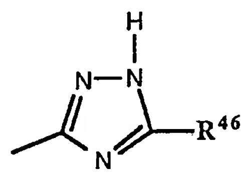
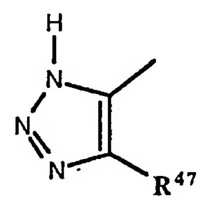
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

52. The composition of Claim 51 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH{=}CH$, $C_3H_7(N)$, SC_3H_7,  CH_2, , C_2H_5, $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9,  CH_2S , $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH-$; wherein R^1 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO, CH_2CO_2H, $CH(CH_3)CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$, $-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H, $-CH_2CH_2-CO-N$O, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2CH_2CH_2F$, $-CH_2SH$ and $-CH_2O-$; wherein R^2 is selected from H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl;

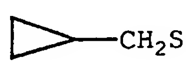
wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

 ,  and 

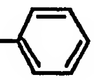
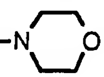
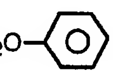
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

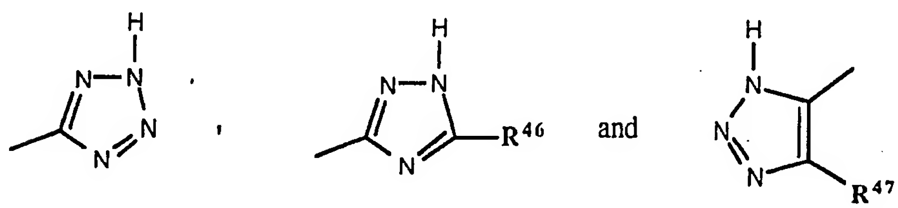
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

53. The composition of Claim 51 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH{=}CH$, $C_3H_7(N)$, SC_3H_7, , , C_2H_5, $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9,  , $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH-$;

wherein R^1 is selected from H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected from amino, aminomethyl, aminoethyl,

aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO, CH_2CO_2H, $CH(CH_3)CO_2H$, , $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$, $-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H, $-CH_2CH_2-CO-$, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2CH_2CH_2F$, $-CH_2SH$ and $-CH_2O-$;

wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,



wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

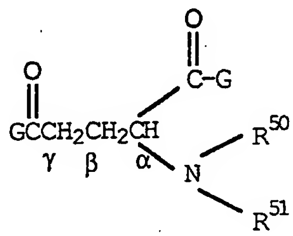
with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

54. The composition of Claim 43 wherein said second residue forms a kidney-enzyme-cleavable amide bond

with the residue of said angiotensin II antagonist compound.

55. The composition of Claim 54 wherein said second residue is provided by a compound of Formula II:



(II)

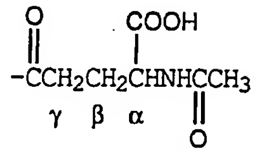
wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{52}$, $-SR^{53}$ and $>NR^{54}$ with each of R^{52}, R^{53} and R^{54} independently selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

56. The composition of Claim 55 wherein each G substituent is hydroxy.

57. The composition of Claim 56 wherein each G substituent is hydroxy; wherein R^{50} is hydrido; and wherein R^{51} is selected from

$-\overset{O}{\overset{\|}{C}}R^{55}$ wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

58. The composition of Claim 57 wherein said second residue is

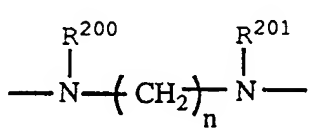


59. The composition of Claim 43 wherein said first residue is an angiotensin II antagonist compound containing a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

60. The composition of Claim 43 wherein said first residue is an angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

61. The composition of Claim 60 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

62. The composition of Claim 61 wherein said diamino-terminated linker group is a divalent radical of Formula III:



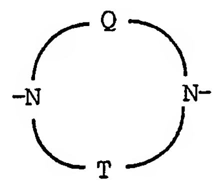
(III)

wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino,

monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

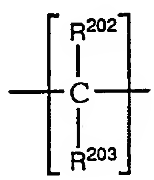
63. The composition of Claim 62 wherein each of R^{200} and R^{201} is hydrido.

64. The composition of Claim 61 wherein said diamino-terminated linker group is a divalent radical of Formula IV:

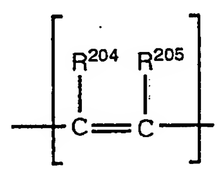


(IV)

wherein each of Q and T is one or more groups independently selected from

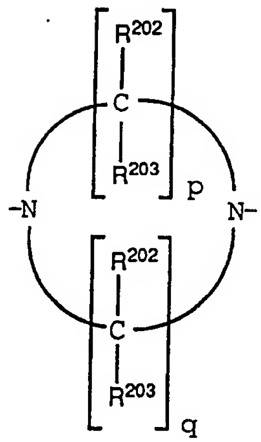


and



wherein each of R^{202} through R^{205} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

65. The composition of Claim 64 wherein said diamino-terminated linker group is a divalent radical of Formula V:



(V)

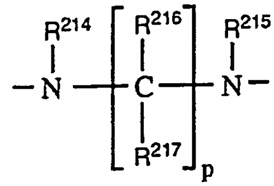
wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

66. The composition of Claim 65 wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

67. The composition of Claim 66 wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

68. The composition of Claim 67 wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two.

69. The composition of Claim 61 wherein said diamino-terminated linker group is a divalent radical of Formula VI:



(VI)

wherein each of R^{214} through R^{217} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

70. The composition of Claim 69 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.

71. The composition of Claim 70 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido and alkyl; and wherein p is two.

72. The composition of Claim 71 wherein each of R^{214}, R^{215}, R^{216} and R^{217} is hydrido; and wherein p is two.

73. The composition of Claim 52 wherein said angiotensin II antagonist compound is 4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

74. The composition of Claim 73 wherein said conjugate is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

75. The composition of Claim 73 wherein said conjugate is N^2-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine.

76. The composition of Claim 73 which is N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide.

77. The composition of Claim 53 wherein said angiotensin II antagonist compound is 4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

78. The composition of Claim 77 which is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

79. The composition of Claim 77 which is N^2-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine.

80. The composition of Claim 77 which is N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide.

81. A method for treating a hypertensive-related disorder or a sodium-retaining disorder, said method comprising administering to a patient afflicted with

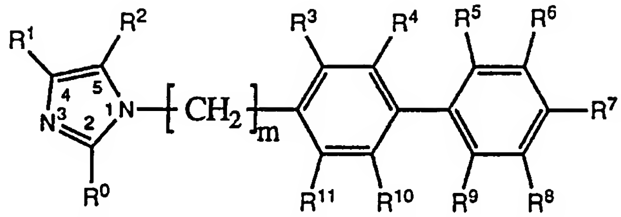
or susceptible to said disorder a therapeutically-effective amount of a renal-selective conjugate, said conjugate comprising a residue of an angiotensin II antagonist compound.

82. The method of Claim 81 wherein said conjugate comprises a first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is provided by an angiotensin II antagonist compound, and wherein said second residue is capable of being cleaved from said first residue.

83. The method of Claim 82 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

84. The method of Claim 83 wherein said angiotensin II antagonist compound providing said first residue is selected from biphenylmethyl 1H-substituted-1,3-imidazole compounds.

85. The method of Claim 84 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:

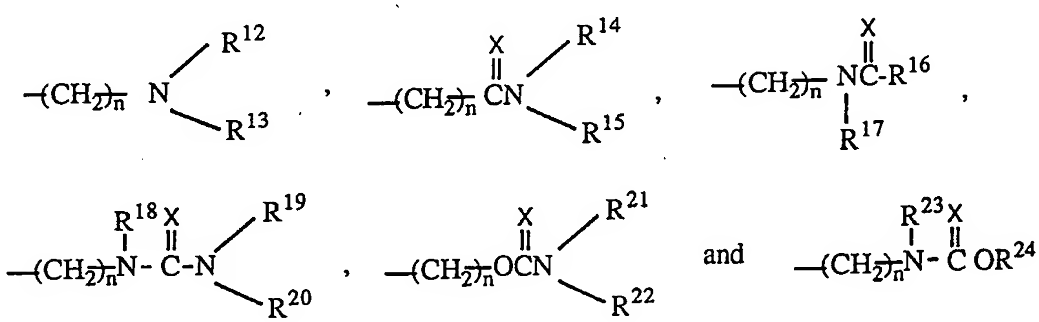


(I)

wherein m is a number selected from one to four, inclusive;

wherein each of R^0 through R^{11} is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing groups has one or more ring atoms selected from oxygen,

sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

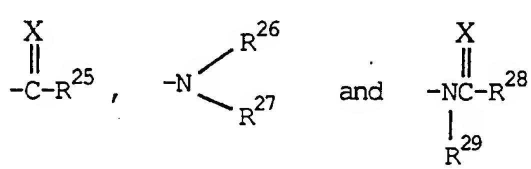
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{16} and R^{17} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

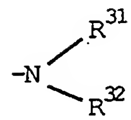
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

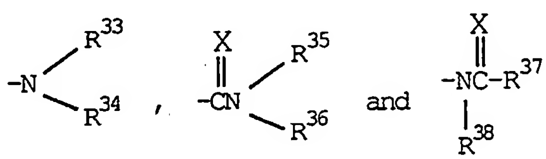
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR^{30} and



wherein D is selected from oxygen atom and sulfur atom and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each of R^{33}, R^{34}, R^{35}, R^{36}, R^{37} and R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R^{26} and R^{27} taken together and R^{28} and R^{29} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{26} and R^{27} taken together and R^{31} and R^{32} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical

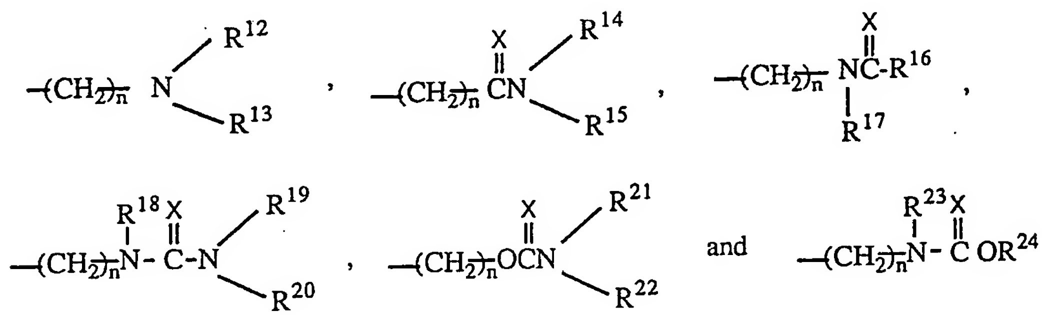
and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

86. The method of Claim 85 wherein m is one; wherein each of R^0 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has

one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

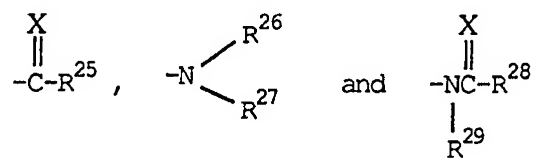
and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

$$-Y_nA$$

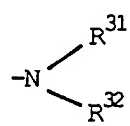
wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl,

cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

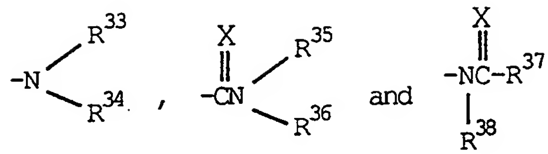
and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

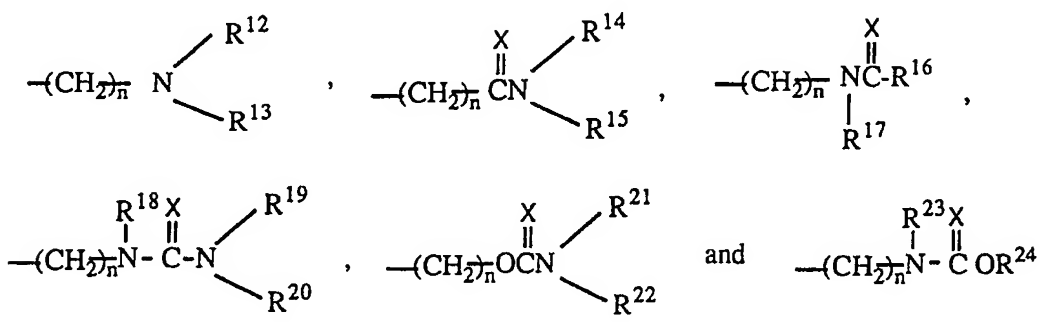
wherein each of R^{26} through R^{31} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

87. The method of Claim 86 wherein m is one; wherein each of R^0 through R^{11} is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalklylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms

selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen taom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

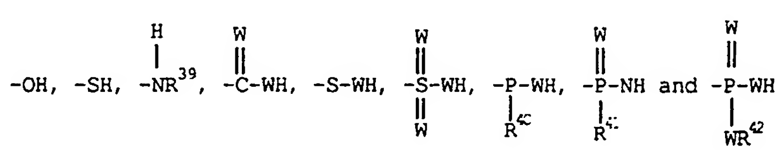
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and erein each of R^3 through R^{11} may be an acidic moiety further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

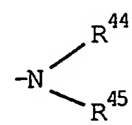
$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{40}, R^{41}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39}, R^{40}, R^{41} and R^{42} may be further independently selected from amino radicals of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R^{40} and R^{41} may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which

heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing R^1 through R^{24}, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula

$$-\overset{\overset{\displaystyle X}{\|}}{C}-R^{25}, \quad -N\begin{array}{l}\diagup R^{26}\\ \diagdown R^{27}\end{array} \quad \text{and} \quad -\underset{\underset{\displaystyle R^{29}}{|}}{N}\overset{\overset{\displaystyle X}{\|}}{C}-R^{28}$$

wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR^{30} and

$$-N\begin{array}{l}\diagup R^{31}\\ \diagdown R^{32}\end{array}$$

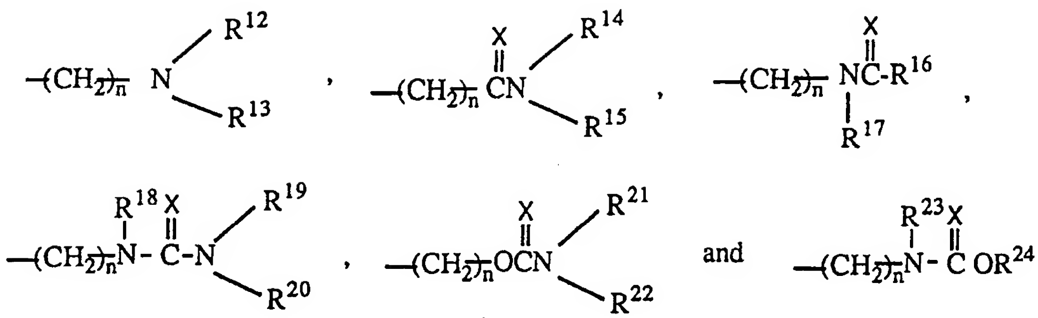
wherein D is selected from oxygen atom and sulfur atom, wherein R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

wherein each of R^{26}, R^{27}, R^{28}, R^{29}, R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

88. The method of Claim 87 wherein m is one; wherein each of R^0, R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

$$-OH,\ -SH,\ -\overset{\overset{\displaystyle H}{|}}{N}R^{39},\ -\overset{\overset{\displaystyle W}{\|}}{C}-WH,\ -S-WH,\ -\underset{\underset{\displaystyle W}{\|}}{\overset{\overset{\displaystyle W}{\|}}{S}}-WH \text{ and } -\underset{\underset{\displaystyle WR^{42}}{|}}{\overset{\overset{\displaystyle W}{\|}}{P}}-WH$$

wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula

$$-N\begin{matrix} \nearrow R^{44} \\ \searrow R^{45} \end{matrix}$$

wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which

heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

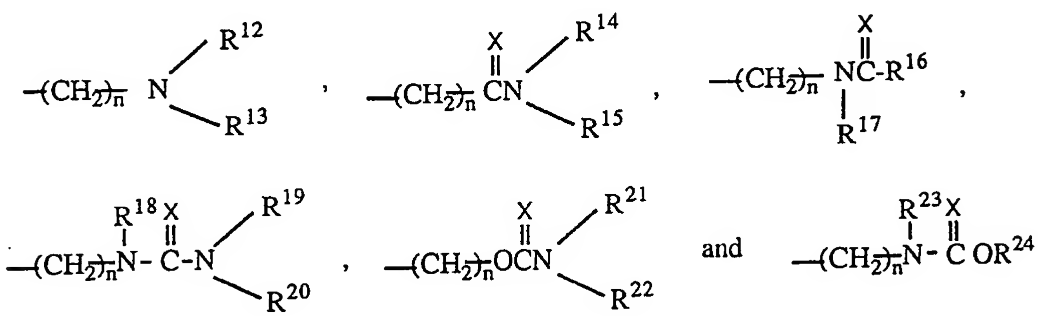
wherein each of R^1 through R^{24}, Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

89. The method of Claim 88 wherein m is one; wherein each of R^0, R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido,

phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

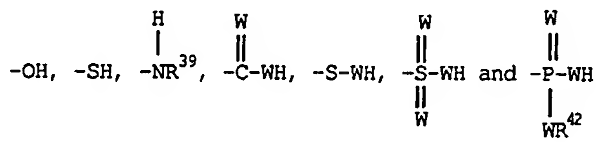
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

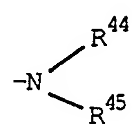
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

$$-Y_nA$$

wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43}; wherein each of R^{39}, R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of

the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

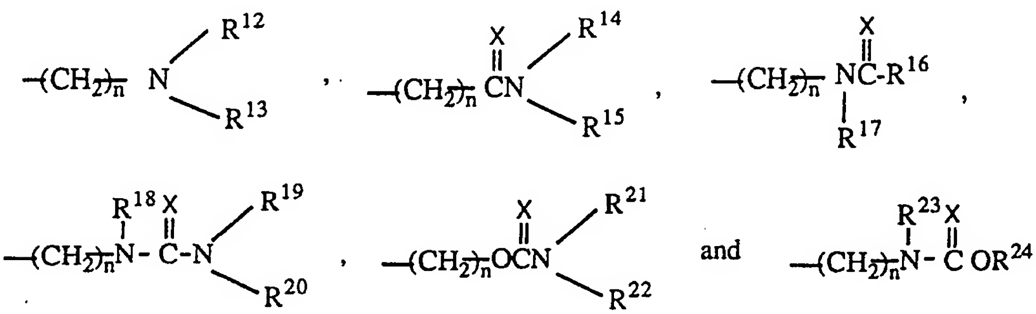
wherein each of R^1 through R^{24}, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24}, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

90. The method of Claim 89 wherein m is one; wherein R^0 is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of R^1 and R^2 is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole,

tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



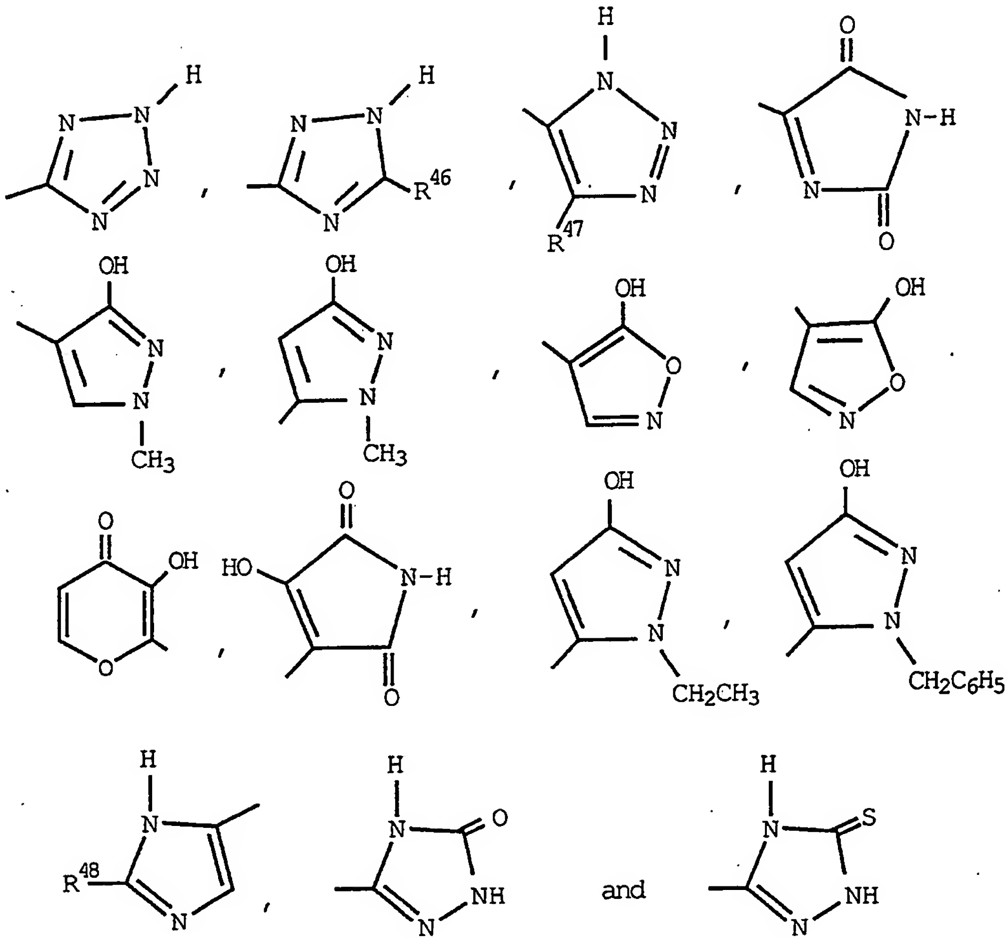
wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

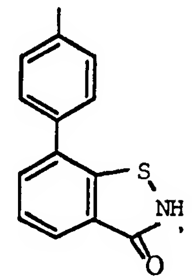
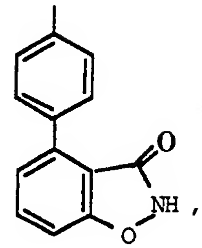
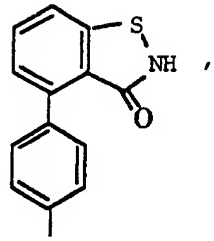
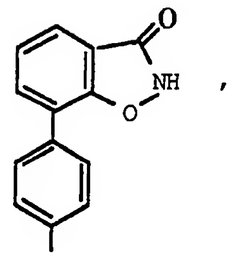
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

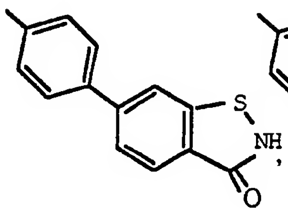
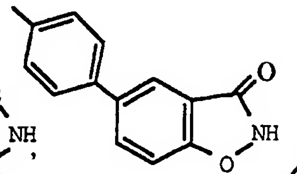
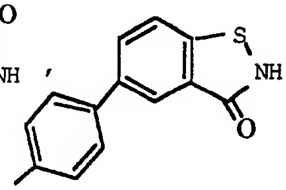
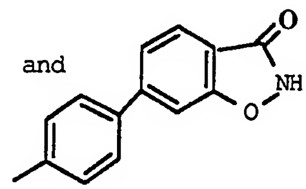
wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties consisting of CO_2H, CO_2CH_3, SH, CH_2SH, C_2H_4SH, PO_3H_2, $NHSO_2CF_3$, $NHSO_2C_6F_5$, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, $CONHOCH_3$, $CONHOC_2H_5$, $CONHCF_3$, OH, CH_2OH, C_2H_4OH, OPO_3H_2, OSO_3H ,



wherein each of R^{46}, R^{47} and R^{48} is independently selected from H, Cl, CN, NO_2, CF_3, C_2F_5, C_3F_7, CHF_2, CH_2F, CO_2CH_3, $CO_2C_2H_5$, SO_2CH_3, SO_2CF_3 and $SO_2C_6F_5$; wherein Z is selected from O, S, NR^{49} and CH_2; wherein R^{49} is selected from hydrido, CH_3 and $CH_2C_6H_5$; and wherein said acidic moiety may be a heterocyclic acidic group attached at any two adjacent positions of R^3 through R^{11} so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from

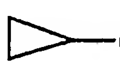
, , , ,

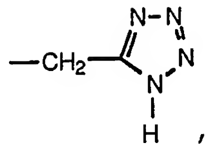
, ,  and 

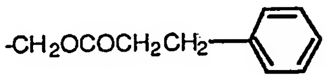
and the esters, amides and salts of said acidic moieties;

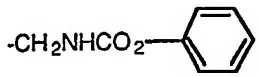
with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

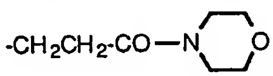
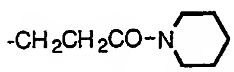
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

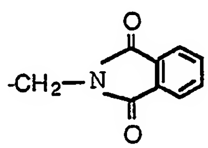
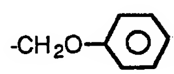
91. The method of Claim 90 wherein m is one; wherein R^0 is selected from C_4H_9(n), $CH_3CH_2CH{=}CH$, C_3H_7(N), SC_3H_7, CH_2, , C_2H_5, C_5H_{11}(n), C_6H_{13}(n), SC_4H_9, CH_2S, $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH$-; wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO,

CH_2CO_2H, $CH(CH_3)CO_2H$, NO_2, Cl,  ,

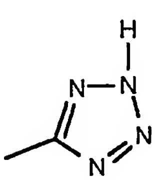
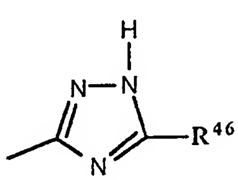
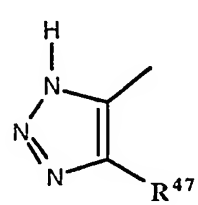
, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,

$-CH_2-NHCO_2C_2H_5$, , $-CH_2NHCO_2CH_3$, -$CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H,

, , $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2OCSNHCH_3$, $-CH_2NHCSOC_3H_7$,

$-CH_2CH_2CH_2F$, $-CH_2ONO_2$, , $-CH_2SH$, ,

92. Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

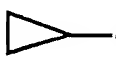
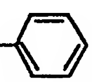
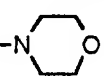
 ,  and 

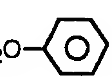
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

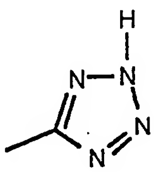
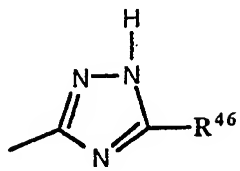
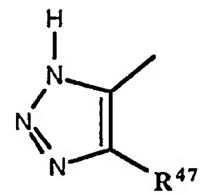
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

92. The method of Claim 91 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH{=}CH$, $C_3H_7(N)$, SC_3H_7, 

,  , C_2H_5, $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9,  CH_2S , $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH$-; wherein R^1 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO, CH_2CO_2H, $CH(CH_3)CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$, $-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2$–  , $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H, $-CH_2CH_2-CO$— 

, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2CH_2CH_2F$, $-CH_2SH$ and $-CH_2O$– ; wherein R^2 is selected from H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluorcpropyl, 1,1-difluorobutyl and 1,1-difluoropentyl;

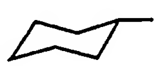
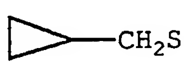
wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,


,

and


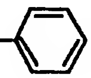
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

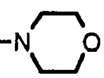
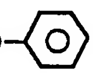
with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

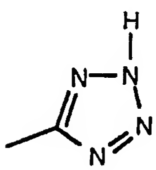
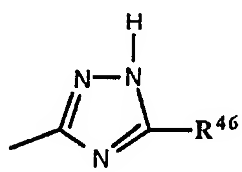
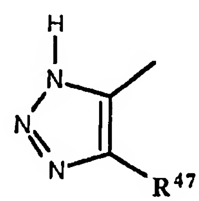
93. The method of Claim 91 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH{=}CH$, $C_3H_7(N)$, SC_3H_7, , , C_2H_5, $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9,  , $CH_3CH{=}CH$ and $CH_3CH_2CH_2CH{=}CH-$; wherein R^1 is selected from H, Cl, NO_2, CF_3, CH_2OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH, CH_2OCOCH_3, CH_2Cl, Cl, CH_2OCH_3, $CH_2OCH(CH_3)_2$, I, CHO,

CH_2CO_2H, $CH(CH_3)CO_2H$, , $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,

$-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2-adamantyl, $-CH_2NHCO_2$-(1-napthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$(1-napthyl), $-CH_2NHCONH$(1-adamantyl), CO_2H,

$-CH_2CH_2-CO-$, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2CH_2CH_2F$, $-CH_2SH$ and $-CH_2O-$;

wherein each of R^3 through ^{11} is hydrido, with the proviso that at least one of R^5, R^6, R^8 and R^9 is an acidic group selected from CO_2H, SH, PO_3H_2, SO_3H, $CONHNH_2$, $CONHNHSO_2CF_3$, OH,

 ,  and 

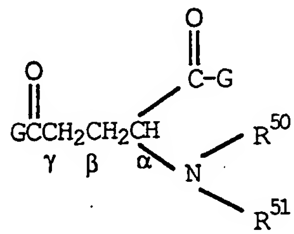
wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2, CF_3, CO_2CH_3 and SO_2CF_3;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

94. The method of Claim 83 wherein said second residue forms a kidney-enzyme-cleavable amide bond with the residue of said angiotensin II antagonist compound.

95. The method of Claim 94 wherein said second residue is provided by a compound of Formula II:



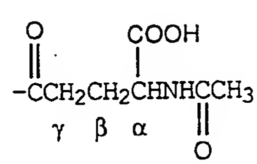
(II)

wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{52}$, $-SR^{53}$ and $>NR^{54}$ with each of R^{52}, R^{53} and R^{54} independently selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

96. The method of Claim 95 wherein each G substituent is hydroxy.

97. The method of Claim 96 wherein each G substituent is hydroxy; wherein R^{50} is hydrido; and wherein R^{51} is selected from $-\overset{\overset{O}{\|}}{C}R^{55}$ wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

98. The method of Claim 97 wherein said second residue is

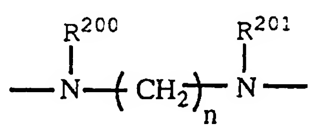


99. The method of Claim 83 wherein said first residue is an angiotensin II antagonist compound containing a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

100. The method of Claim 83 wherein said first residue is an angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

101. The method of Claim 100 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

102. The method of Claim 101 wherein said diamino-terminated linker group is a divalent radical of Formula III:

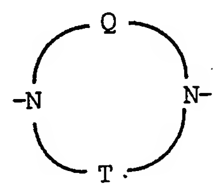


(III)

wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

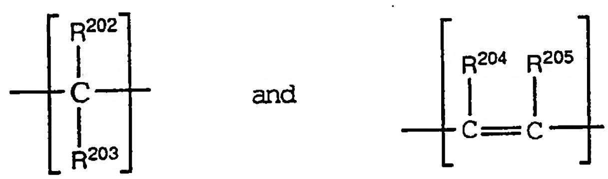
103. The method of Claim 102 wherein each of R^{200} and R^{201} is hydrido.

104. The method of Claim 101 wherein said diamino-terminated linker group is a divalent radical of Formula IV:



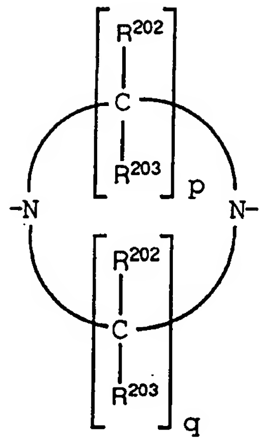
(IV)

wherein each of Q and T is one or more groups independently selected from



wherein each of R^{202} through R^{205} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

105. The method of Claim 104 wherein said diamino-terminated linker group is a divalent radical of Formula V:



(V)

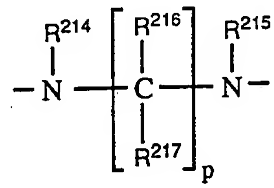
wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

106. The method of Claim 105 wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

1‿7. The method of Claim 106 wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

108. The method of Claim 107 wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two.

109. The method of Claim 101 wherein said diamino-terminated linker group is a divalent radical of Formula VI:



(VI)

wherein each of R^{214} through R^{217} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

110. The method of Claim 109 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.

111. The method of Claim 110 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido and alkyl; and wherein p is two.

112. The method of Claim 111 wherein each of R^{214}, R^{215}, R^{216} and R^{217} is hydrido; and wherein p is two.

113. The method of Claim 92 wherein said angiotensin II antagonist compound is 4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

114. The method of Claim 113 wherein said conjugate is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

115. The method of Claim 113 wherein said conjugate is N^2-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine.

116. The method of Claim 113 which is N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide.

117. The method of Claim 93 wherein said angiotensin II antagonist compound is 4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

118. The method of Claim 117 which is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

119. The method of Claim 117 which is N^2-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine.

120. The method of Claim 117 which is N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide.

121. The method of Claim 81 wherein said hypertensive-related disorder is chronic hypertension.

122. The method of Claim 81 wherein said sodium-retaining disorder is congestive heart failure.

123. The method of Claim 81 wherein said sodium-retaining disorder is cirrhosis.

124. The method of Claim 81 wherein said sodium-retaining disorder is nephrosis.

Chronic Infusion of Example #81 Conjugate

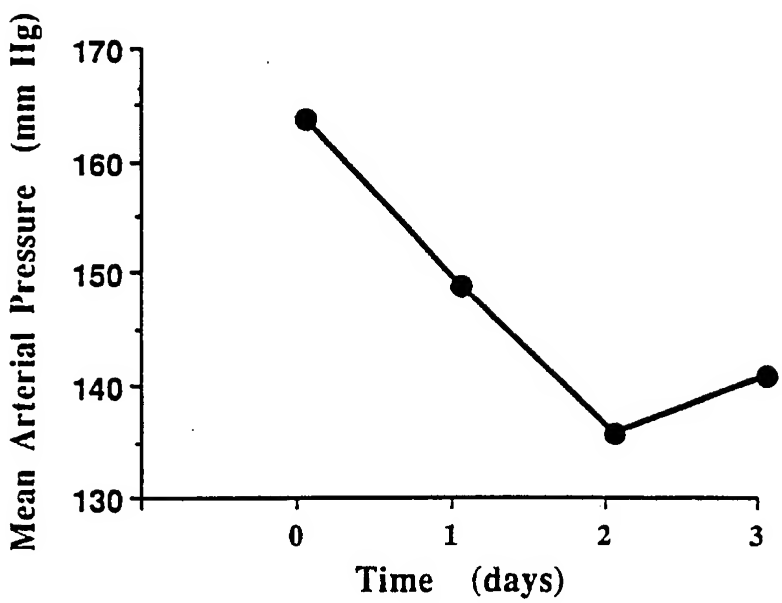


Figure 1

Acute Angiotensin II Pressor Response During Chronic Infusion of Example #81 Conjugate

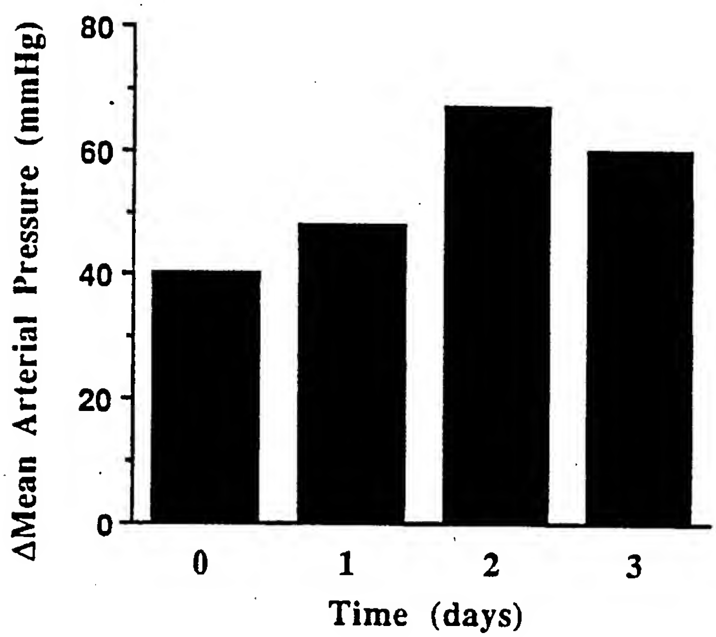


Figure 2

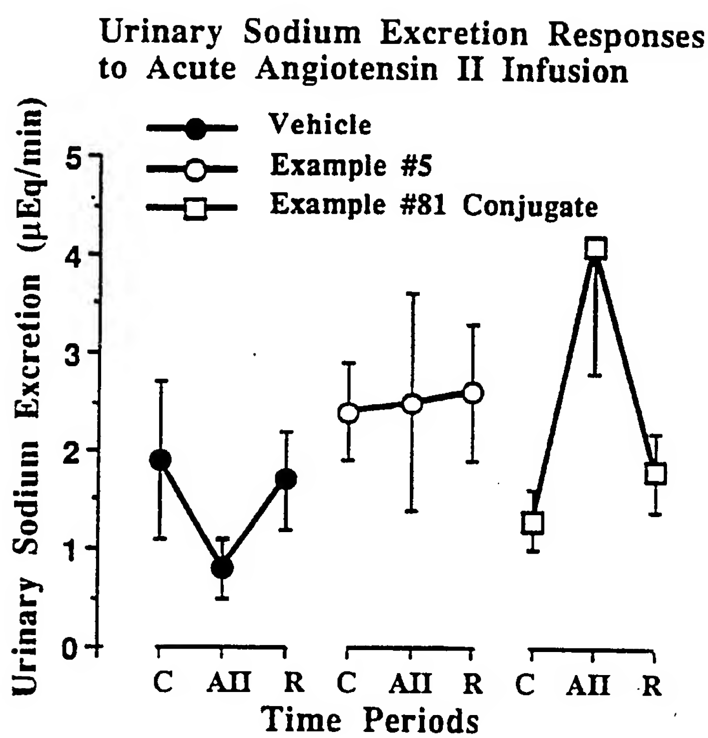

Urinary Sodium Excretion Responses
to Acute Angiotensin II Infusion
Vehicle
Example #5
Example #81 Conjugate
Urinary Sodium Excretion (µEq/min)
0
1
2
3
4
5
C
AII
R
C
AII
R
C
AII
R
Time Periods

Figure 3

Mean Arterial Pressure Responses to Acute Angiotensin II Infusion

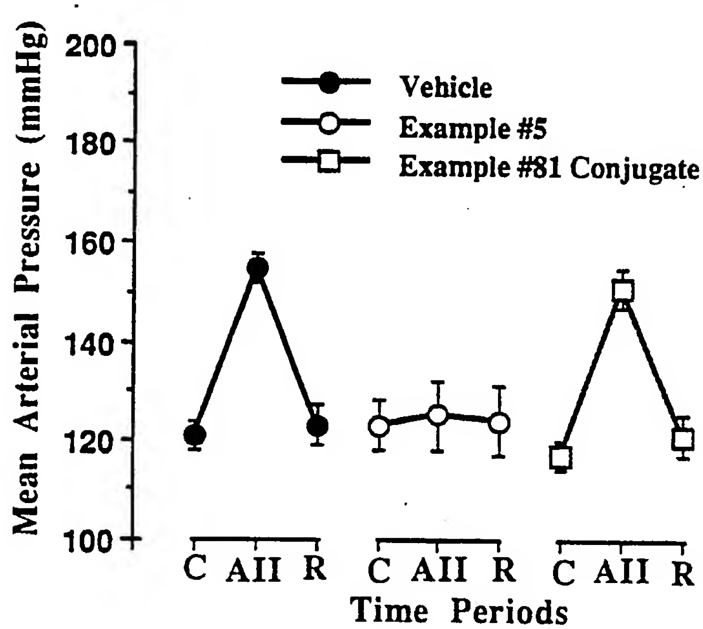


Figure 4